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ON THE FREQUENT FAILURE OF THE URINE TO DECOMPOSE IN CASES OF PULMONARY TUBERCULOSIS.

By

W. HALE WHITE AND H. I. JANMAHOMED.

(From the Laboratories, Guy's Hospital.)

In 1892 one of us pointed out that the urine of patients having pulmonary tuberculosis often remained acid for a very long time. Out of 182 specimens examined, 4 remained acid for over one hundred days, 3 between fifty and one hundred days, 14 between thirty and fifty days, 24 between twenty and thirty days, 19 between fifteen and twenty days, 32 between ten and fifteen days, 50 between five and ten days, and 36 less than five days. The acidity of the urine was roughly tested in a few cases, and the results suggested that in this disease the acidity is sometimes unusually high. We have recently re-examined this matter and have confirmed the original observation, for, on looking at Table I, it will be seen that 29 separate specimens of urine collected, with one or two exceptions, for the whole twenty-four hours, were obtained from eight cases of pulmonary tuberculosis. Two specimens remained acid two days: 1, three days; 1, five days; 2, eight days; 2, ten days; 2 twelve days; 3, fifteen days; 2, sixteen days; 2, seventeen days;

1, nineteen days ; 3, twenty days ; 1, twenty-five days ; 1, twenty-seven days ; and 1, twenty-eight days.   Specimen No. 3 (Case 1) was still acid one hundred and fifteen days after it was passed. Specimen No. 5 (Case 2) was still acid one hundred and thirty-five days after it was passed.   Specimen No. 8 (Case 3) was still acid one hundred and eight days after it was passed.   The specimen from Case 7 was still acid fifty days after it was passed, and No. 2 from Case 8, was still acid twenty-seven days after it was passed.   All the specimens on which the observations recorded in this paper were made, whether from sufferers from phthisis or any other disease, were collected during the cold weather of December, January or February.

The acidity was always estimated by Folin's method.   Twenty cubic centimetres of urine were measured into an Erlenmeyer's flask.   To this 15 to 20 grms. of potassium oxalate were added to saturate it, and then two drops of phenolphthalein solution. A decinormal soda solution was then dropped in until a change of colour to a faint pink appeared, the flask being frequently shaken.   A control flask containing a little of the same urine saturated with potassium oxalate was always prepared so that the first change to a slight pink in the first flask could be readily seen. As a rule two estimations of each specimen were made, and the result was not taken as correct unless the difference between the two estimations was not more than 0·1 c.c. of decinormal soda solution. · The acidity was always expressed as the number of cubic centimetres of decinormal NaOH needed to neutralize 20 c.c. of the urine in question.

The acidity (see Table I) of nineteen specimens of urine from patients suffering from other diseases than pulmonary tuberculosis was also tested, and the following figures show the acidity of these nineteen contrasted with that of the twenty-nine specimens from cases of pulmonary tuberculosis.   In every case the urine was tested almost directly after it was passed.   Our figures should not be compared with Folin's, for his represent the number of cubic centimetres of decinormal soda solution required to neutralize 25 c.c. of urine, ours the number necessary to

neutralize 20 c.c. of urine, and the specific gravity of his specimens was higher than that of ours.

	Cases of Pulmonary Tuberculosis.	Other Cases.
30 c.c. decinormal NaOH required to neutralize 20 c.c. urine	1	0
11 c.c.	1	0
10 c.c. or over, but under 11 c.c. ...	2	0
9 c.c. „ „ 10 c.c. ...	5	0
8 c.c. „ „ 9 c.c. ...	5	0
7 c.c. „ „ 8 c.c. ...	1	1
6 c.c. „ „ 7 c.c. ...	7	3
5 c.c. „ „ 6 c.c. ...	3	3
4 c.c. „ „ 5 c.c. ...	1	9
3 c.c. „ „ 4 c.c. ...	0	2
2 c.c. „ „ 3 c.c. ..	3	1
	29	19

Thus we see that in twenty-five out of twenty-nine specimens of fresh urine from cases of pulmonary tuberculosis the acidity was 5 or more, but in only seven out of nineteen specimens of fresh urine from patients who were suffering from other diseases than pulmonary tuberculosis was the acidity 5 or more. Further, among those who were not sufferers from pulmonary tuberculosis, the acidity was never over 8, but of the specimens from those who had this disease the acidity was over 8 in fourteen, or virtually 50 per cent. It is particularly worthy of note that among those who were not suffering from tuberculous disease of their lungs, two were cases of tuberculous peritonitis and one of Addison's disease. These three patients were responsible for nine specimens of urine; the acidity of one was 5, but the remaining eight were all under this figure. No other cases of tuberculosis in which the lungs were free happened to come under our notice while these observations were being made, but as far as the figures before us go they strongly suggest that this high acidity of the urine is not met with in tuberculous disease unless the lungs are affected. It will be noticed that the nine specimens of urine

from the two cases of tuberculous peritonitis and the case of Addison's disease all decomposed quickly, three in four days, one in three days, four in two days, and one in one day.

As the cases of tuberculous disease of the lungs were all in-patients, and therefore all severely ill, it was thought that perhaps the frequent failure of the urine to decompose was common to any severe infectious disease ; so seven specimens of urine from four cases of acute pneumonia and three from a case of staphy-lococcal septicæmia were examined ; but all ten specimens quickly decomposed, one remaining acid five days, three four days, three three days, and three two days. The highest acidity was 7·2, in three specimens it was 6 or over, in two it was 5 or over, and in four between 4 and 5. This somewhat high acidity is probably merely the result of the concentration of the urine, for all these patients had considerable pyrexia, but the acidity was far below that frequently met with in pulmonary tuber-culosis, and none of these ten specimens of urine remained acid an unusually long while. It appears, therefore, we may conclude that the extremely slow decomposition of the urine frequently met with in some cases of tuberculosis of the lungs is, as far as is at present known, peculiar to that disease, in which also the urine is very often exceptionally acid.

We will now consider in more detail these two strange pecu-liarities of the urine of sufferers from pulmonary tuberculosis. Speaking generally, the more highly concentrated a urine is, the more acid it is ; but we have just seen that five patients suffering from an acute febrile disease, and therefore passing concentrated urine, did not any of them pass urine as acid as is commonly the case in tuberculous disease of the lungs, and a reference to Case 3 is alone enough to show that in tuberculous disease of the lungs some other circumstance than concentration of the urine is necessary to explain its high acidity, for out of eight specimens examined the acidity was never under 8, and twice it was 10, but the specific gravity never exceeded 1·014, and was in four specimens under 1·009. Again, we notice in Case 3 a specific gravity of 1·008 with an acidity of 10, and in Case 4 the same specific gravity with an acidity of 2·5. It is true that in Case 5,

in which the very high acidity of 30 was attained, the specific gravity was 1·040, but from the considerations just given we are bound to conclude that some other factor or factors than specific gravity have to do with the high acidity of the urine seen in tuberculous disease of the lungs. No doubt the specific gravity plays its part, although a minor part.

It is well known that when oxidation is deficient in the body there is an accumulation of lactic acid which is excreted in the urine. We thought it just possible that as in these cases there was extensive disease of the lungs there might be deficient oxidation with a considerable excretion of lactic acid in the urine, and hence its high acidity, although such a view was unlikely, for the urine of the patients suffering from pneumonia did not show nearly as great acidity as those who had tuberculous disease of the lungs. The estimation of lactic acid in the urine requires special care, and we were fortunate in getting Mr. J. H. Ryffel, who has devoted particular attention to this, kindly to do some analyses for us. He tells us that by the Hopkins thiophene test he found no lactic acid in these urines, which were highly acid and did not decompose for many days, and certainly if any was present the amount was too minute to explain the high acidity or the failure of the urine to decompose. This result is of interest, for Jerusalem, by his method, found a small quantity of lactic acid in the urine of a patient with pulmonary tuberculosis. As far as we have been able to investigate the matter, we are therefore quite in the dark as to the cause of this peculiar high acidity of the urine that we are describing. Apparently tuberculous disease of pulmonary tissue leads to the formation of an unknown body or bodies which keep the urine highly acid, retard its decomposition, sometimes for over a hundred days, and, as we shall show presently, retard the formation of ammonia.

The obvious thought comes to one's mind that the failure to decompose is dependent upon the high acidity, and perhaps this is so to some extent. For example, three specimens from Case 4 decomposed in two, three, and two days respectively, and in all the acidity was only between 2 and 3; these urines decomposed more quickly than any from the other patients suffering from

tuberculous disease of the lungs, and they had the lowest acidity. But there is no direct constant ratio between the acidity and the rate of decomposition. For example, in Case 1, a specimen, the acidity of which was 5·6, decomposed in sixteen days; and one, the acidity of which was 5·5, was still acid at the end of a hundred and fifteen days. In Case 2 there is some association between the failure to decompose and the acidity, but it is very irregular; thus a urine with an acidity of 7·2 went alkaline in twenty-five days, and one with an acidity very little higher, viz., 8·4, was still acid at the end of a hundred and thirty-five days. In Case 3 it happened that three specimens had an acidity of 9·9 ; two went alkaline in twenty days and fifteen days respectively, but the third was still acid at the end of a hundred and eight days, and a specimen with an alkalinity of 10·2 turned acid in nineteen days. In Case 5 the specimen with the very high acidity of 30 turned alkaline in five days, but a specimen with an acidity of 8·3 remained acid eight days. Case 7 had the high acidity of 11, and was still acid at the end of fifty days; but again the attempt to establish any direct relationship is frustrated in Case 8, for the acidity of the two specimens was virtually identical, yet one turned alkaline in twelve days, the other was still acid at the end of twenty-seven. But this discrepancy between the acidity of the urine and the time during which it remains acid is equally striking in the urines which were obtained from patients suffering from other diseases than tuberculous disease of the lungs. For example, in one case of tuberculous peritonitis the urine with the highest acidity remained acid longest, and in the other the urine with the lowest acidity remained acid longest ; in the first case of lobar pneumonia the urine with the highest acidity remained acid longest, and in the second case that with lower acidity remained acid longest. Another way of showing the want of relationship between the acidity and the time during which the urine remains acid is to contrast the second and third cases in Table I. If in both we disregarded the one specimen which was still acid when this paper was written, we find that the average acidity in Case 2 was 6·48, that in Case 3, 9.31, yet on the average the urine remained

acid 20·4 days in Case 2 and only eighteen days in Case 3, although in this the acidity was much greater. Therefore we learn that while the urine of patients with tuberculous disease of the lungs is often excessively acid and remains acid an unusually long while, yet no direct relationship can be traced between the excess of acid and the duration of the acidity.

We have in the table below compared the specific gravity with the number of days the urine remained acid in the eight cases of pulmonary tuberculosis (twenty-nine specimens).

Sp. gr.	No. of Specimens.	Days each specimen remained acid.
1·006	1	Still acid at end of 108.
1·007	2	Still acid at end of 115, 12.
1·008	5	28, 15, 10, 2, 2.
1·009	2	25, 10.
1·010	4	27, 19, 16, 3.
1·011	2	20, 20.
1·012	2	20, 17.
1·014	3	Still acid at end of 50, 16, 15.
1·015	2	Still acid at end of 135, 15.
1·016	1	12.
1·018	2	Still acid at end of 27, 17.
1·023	1	8.
1·025	1	8.
1·040	1	5.

We see that the specific gravity of the urine in these cases was unusually low, and it is worthy of note that in Case 4, in which the specific gravity was 1·008, 1·010, and 1·008 in the three specimens, the acidity was very low, viz.: 2·5, 2·6, and 2·9, and these three specimens decomposed in two, three, and two days respectively, so it may be that the prolonged acidity of the urine from some patients affected with tuberculous disease of the lungs is dependent in some degree on a high acidity associated with a low specific gravity ; but there is no direct relationship between the specific gravity and the duration of acidity, for one specimen with a specific gravity of 1·006 was still acid at the end of a hundred and eight days, and one with a specific gravity of 1·015

was still acid at the end of a hundred and thirty-five days. On the other hand, two specimens with a specific gravity of 1·008 decomposed in two days, and one with a specific gravity of 1·040 turned alkaline in five days.

In the three first cases in Table I the acidity was estimated, not only when the urine was fresh, but again at the end of two days, at the end of seven days, and at the end of fourteen days. Reference to the tables shows that invariably the acidity slowly fell, but the rate of fall was not the same in all the cases. In Case 2 a specimen which had an acidity as high as 5·2 at the end of fourteen days was still acid at the end of a hundred and thirty-five days, and in Case 3 one that had an acidity of 5 at the end of fourteen days was still acid at the end of a hundred and eight days; further, a specimen from Case 3 which had an acidity of 5 at the end of fourteen days, remained acid twenty-eight days. These figures appear to show that if at the end of a fortnight the acidity is still high the urine will remain acid a long while, but that the converse statement is not correct is shown by the fact that specimen 3 from Case 1 only had an acidity of 0·7 at the end of fourteen days, yet after a hundred and fifteen days it was still acid, and specimen 1 from Case 2, at the end of fourteen days had an acidity of 2·0 and remained acid twenty-five days, although specimen 3 from Case 3, having at the end of the same time an acidity of 4·9, only remained acid fifteen days.

The fact that the urines from patients suffering from tuber-culous disease of the lungs may remain acid for so long naturally led us to investigate the rate of growth of bacteria in them. The urines of Cases 2 and 8 were examined from this point of view. Each patient was carefully searched to make sure that no disease of the genito-urinary apparatus existed, and catheter specimens were taken with full precautions against infection of the urine from without. Specimens of the urine incubated at 37° C. for three days remained sterile. A tube containing 5 c.c. of the urine to be examined was taken, and also one containing 5 c.c. of sterile broth. Each was inoculated with a loopful of a young twenty-hours culture in broth of the bacillus coli communis. Next, gelatine tubes were inoculated with a loopful of the broth

and urine respectively and then plated out on gelatine at the end
of five minutes, fifteen minutes, thirty minutes, one hour, two
hours, and six hours respectively from the inoculation of the
broth and urine by the bacillus coli communis. The gelatine
plates were kept at the room temperature for a week and the
number of colonies on each were then counted. The results are
shown in Table II, and it will be seen that invariably there were
fewer colonies of growth on the plates planted with the bacillus
coli communis from the urine than in the plates planted from the
broth ; in other words, the urine from patients with pulmonary
tuberculosis has considerable bactericidal power. To take
examples at random. In experiment 1, at the end of thirty
minutes there were 124 colonies surviving from the broth inocu-
lation, and only 58 from the urine inoculation. In experiment 2
at the end of six hours there were 130 colonies surviving from the
broth inoculation and only 60 from the urine inoculation. In
experiment 3 the respective numbers at the end of six hours were
40 and 12, and in experiment 4 at the end of five minutes 144
and 54. The observations upon the bactericidal properties of
these urines are supported by the observation, made in 1892, that
the urine of patients with pulmonary tuberculosis contained very
few bacilli, even after a considerable time. Yeast-like organisms,
however, grow freely in such urine and moulds grow on it, and
when the urine has remained acid over a month there is often a
considerable mass of moulds on its surface. That the growth
of the moulds is the cause of the acidity is very unlikely, for
moulds also grow on those that turned alkaline, and there was
no sugar in any of these urines from which the moulds could
produce acid.

In the paper published in 1892 it was pointed out that these
urines which remain acid a very long while develop a disagreeable
smell, like rotten cheese. That was also true of the specimens
now being described ; but in 1892 several of the specimens which
remained acid a long while gradually became dark until, after
some months, they were black. But not all underwent this
change, for it was only seen in 19 specimens out of 182 ; so it
may be a mere accident that it has not been observed this time,

or it may be that it was due to some micro-organism which chanced to be present in the air in 1892, but which was not present in 1909. It would be interesting to know whether but few patients with tuberculosis of the lungs suffer from genito-urinary tuberculosis, for perhaps the bactericidal properties of the urine prevent the onset of genito-urinary tuberculosis. Not many cases of tuberculosis do better with tuberculin treatment than those of the genito-urinary tract; perhaps this is in some way connected with the peculiarities of the urine.

The urines from Cases 2 and 3 were examined to see if they contained any opsonins for bacillus coli communis or bacillus tuberculosis. The examination was made in the usual way, but instead of normal serum urine from a healthy person was used, and instead of the serum to be examined for its opsonic index the urine from one of these cases was substituted. In neither the healthy urine nor the urine from the patients with tuberculous disease of the lungs could any opsonins for either the bacillus coli communis or the bacillus tuberculosis be demonstrated. These urines were examined for phenol and indol, but none was found, so that the tardiness of their decomposition cannot have been due to either of these bodies. Abundance of indican was often present; this was probably owing to increased intestinal decomposition. The specimen from Case 2, which was still acid at the end of a hundred and thirty-five days, was examined for ammonia a hundred days after it was passed. It was found to contain 1·407 grms. per litre, the normal in fresh urine being 0·46, which indicates that the acidity is really greater than appears, and also that as the amount of ammonia is so small a large amount of urea is still undecomposed. We have carefully examined the clinical facts noticed about all the patients suffering from pulmonary tuberculosis, whose urine has been used for these observations, and we can detect nothing unusual about them. Case 4, in which the acidity of the urine was so low, and in which this fluid decomposed so much more rapidly than in the other cases, was the only one with an ischio-rectal abscess. Likewise in the series published in 1892 no association between the state of the urine and any particular symptom could be discovered, but

all the cases in that series and in this now published were sufficiently ill to be in the hospital. In every case used for the present paper tubercle bacilli were found in the expectoration, and abundant physical signs were present in the lungs. In no case was any drug used.

We wish to express our best thanks to Dr. J. W. Eyre and Mr. J. H. Ryffel for much help freely given to us.

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TABLE I.

The Acidity is expressed as the number of cubic centimetres of decinormal soda solution necessary to neutralize 20 c.c. of urine.

Patient.	Diagnosis.	Spec. No.	Acidity fresh.	Acidity 2 days.	Acidity 1 week.	Acidity 2 weeks.	How long remained Acid.	Sp. gr.
Case 1	Phthisis	1	4·5	3	1		10 days	1·008
„	„	2	5·6	4·9	2·2	1·1	16 days	1·010
.	„	3	5·5	4·1	2·3	0·7	Still acid at end of 115 days	1·007
Case 2	Phthisis	1	7·2	7·2	6·5	2·0	25 days	1·009
„	„	2	6·4	6·2	5·8	3·2	20 days	1·011
„	„	3	6·2	6·0	5·0	2·2	20 days	1·011
„	„	4	6·4	6·2	6·0	4·1	27 days	1·010
„	„	5	8·4	8·2	8·0	5·2	Still acid at end of 135 days	1·015
„	„	6	6·2	6·0	4·8	2·2	10 days	1·009
Case 3	Phthisis	1	9·9	9·7	6·2	3·1	20 days	1·012
„	„	2	10·2	10	9	4·1	19 days	1·010
„	„	3	9·9	9·2	8·1	4·9	15 days	1·008
„	„	4	10	8·5	7·9	5	28 days	1·008
„	„	5	8			2·2	12 days	1·007
„	„	6	8·2	6·6	4·3	2·1	15 days	1·014
„	„	7	9			4	17 days	1·012
„	„	8	9·9	8·7		5	Still acid at end of 108 days	1·006
Case 4	Phthisis	1	2·5				2 days	1·008
„	„	2	2·6				3 days	1·010
„	„	3	2·9				2 days	1·008

TABLE I. (*continued*).

Patient.	Diagnosis.	Spec. No.	Acidity fresh.	Acidity 2 days.	Acidity 1 week.	Acidity 2 weeks.	How long remained Acid.	Sp. gr.
Case 5	Phthisis	1	30				5 days	1·040
„	„	2	8·3				8 days	1·025
„	„	3	6·9				8 days	1·023
Case 6	Phthisis	1	6·4				15 days	1·015
„	„	2	5·9				16 days	1·014
„	„	3	6·4				17 days	1·018
Case 7	Phthisis	1	11				Still acid at end of 50 days	1·014
Case 8	Phthisis	1	8·8				12 days	1·016
„	„	2	9				Still acid at end of 27 days	1·018
Case 9	Tub. Perit.	1	2·2				2 days	1·012
„	„	2	4				4 days	1·010
„	„	3	3·9				2 days	1·012
Case 10	Tub. Perit.	1	3·2				4 days	1·009
„	„	2	4·3				1 day	1·015
„	„	3	5·0				2 days	1·010
Case 11	Addi- son's Disease	1	4				3 days	1·010
„	„	2	4·9				2 days	1·012
„	„	3	4·2				4 days	1·010
Case 12	Staphyl. Septic.	1	5·9				5 days	1·011
„	„	2	6·2				4 days	1·013
„	„	3	5·4				3 days	1·013
Case 13	Acute Lobar Pneum.	1	6·9				2 days	1·025
„	„	2	7·2				4 days	1·022
„	„	3	6·0				3 days	1·020
Case 14	Acute Lobar Pneum.	1	4·7				2 days	1·015
„	„	2	4·5				4 days	1·013
Case 15	Lobar Pneum.	1	4·2				3 days	1·014
Case 16	Lobar Pneum.	1	4·8				2 days	1·014

TABLE II.—Experiments on the Bactericidal Properties of Urines from patients with Pulmonary Tuberculosis.

Patient.	Expt. No.	Time between Inoculation and Plating.	No. of Colonies surviving in Broth.	No. of Colonies surviving in Urine.
Case 2	1	5 minutes	52	44
„	1	15 minutes	93	62
„	1	30 minutes	124	58
„	1	1 hour	120	52
„	1	2 hours	54	15
„	1	6 hours	44	10
Case 2	2	5 minutes	110	60
„	2	15 minutes	114	64
„	2	30 minutes	130	54
„	2	1 hour	140	69
„	2	2 hours	148	72
„	2	6 hours	130	60
Case 3	3	5 minutes	140	50
„	3	15 minutes	150	53
„	3	30 minutes	100	40
„	3	1 hour	66	30
„	3	2 hours	58	22
„	3	6 hours	40	12
Case 3	4	5 minutes	144	54
„	4	15 minutes	140	58
„	4	30 minutes	90	42
„	4	1 hour	100	46
„	4	2 hours	54	20
„	4	6 hours	44	25

SOME POINTS IN THE TREATMENT OF SEVERE TALIPES.

By

R. P. ROWLANDS, M.S.

It is true that most deformities are either preventable or curable, in their early stages, by safe and simple means. If these points were more widely and thoroughly appreciated, we should not see so many cripples in our streets, and there would be fewer beggars and less poverty. Many cripples, now hopelessly handicapped in the struggle for existence, would be useful members of society. I do not propose to go into the methods of prophylaxis and early treatment here. On the contrary, I wish to describe a neglected example of extreme deformity, and to make a few remarks concerning the treatment of similar cases, which are often regarded as hopeless and uninteresting.

In passing, I wish to lay stress on the enormous importance of patient and long-continued after-treatment of nearly all cases of talipes. Without this care operations and instruments are more or less wasted. In view of the well-known tendency of deformities to recur, I believe that the operative procedures in common use are not radical enough. Too much reliance is placed on tenotomies and similar tinkering measures. It is probable that this false conservatism is a survival of pre-aseptic days, and dependent upon too much fear and too little enterprise. A lack of interest in what appears to be unpromising material may be a

contributory cause.   There prevails an exaggerated view of the danger of extensive operations for talipes, and therefore little is done, or amputation is sometimes advised.

It is certainly difficult to cleanse a deformed foot satisfactorily, but with due care the dangers of infection can be reduced to a minimum.   Moreover, extensive wounds of the soft parts and of the bones heal well, even in paralysed limbs, in spite of a prevailing belief to the contrary.   For several years I have adopted more radical operations with far more success than I ever expected.   The object of this paper is to recommend these methods, some of which, at least, are original.   With time I have gradually learnt to combine a variety of methods in order to be certain of getting a good result.   Some of the steps and precautions may appear trivial, but their importance may be appreciated when gratifying results are obtained.   The value lies in the cumulative effect.   Thus to tenotomies are added division of fasciæ, ligaments, excision of carefully-selected pieces of bone, and redundant skin and other soft parts.   Transplantations of tendons are valuable when combined with other procedures, and when care is taken to relieve the muscles from tension.

I have chosen the following case from a good many, because the simple nature of the severe deformity made it easy to get accurate photographic records of the conditions before and after operation.   Without these photographs it would have been difficult for those who only saw the patient at my clinical lecture* to appreciate the changes that have been wrought by operation.   No one examining the foot as it now is would believe that it could have been so deformed as the photographs prove. (*Vide* figs. 1–4.)   I propose first to describe the case, and then to discuss the various procedures which were adopted in this case, and how these may be modified for other varieties of club foot.

History.—Until he was about three years old, the boy walked naturally, then he had some severe illness, which was followed by paralysis of the left leg and foot.   Very gradually the foot became more and more deformed.   When he was fourteen he

* The patient whose photographs are shown in this paper was shown at a clinical lecture on May 17th, 1909.

Some points in the Treatment of Severe Talipes.

Fig. 4.—J. L. Showing the left foot in good position four months after lengthening the heel tendon and excising the head and neck of the astragalus.
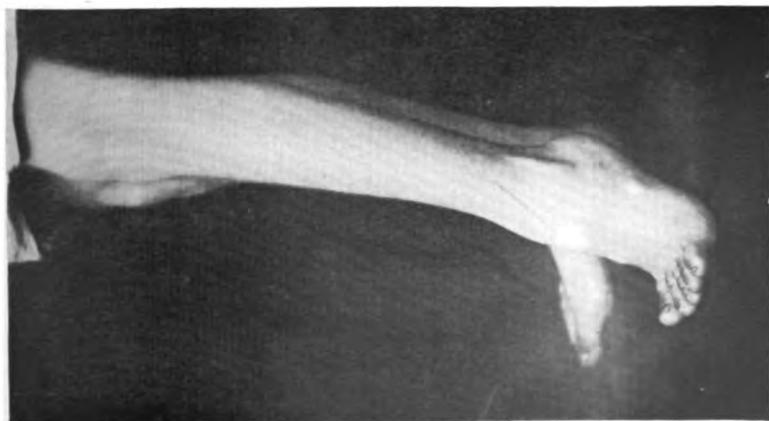
Fig. 1.—J. L. Severe talipes equinus with apparent lengthening of the left limb, unusual prominence of the head of the astragalus, and hyperextension of the toes.

FIG. 2.—J. L. The extreme talipes equinus is well shown with the prominence of the head of the astragalus in front, the scaphoid articulating with its inferior surface only. The head and neck of the bone were removed, the section passing almost vertically. Note the malposition and atrophy of the heel-bone.

FIG. 3.—J. L. The same foot as shown in Fig. 2, but the radiogram has been taken from the outer side, whereas Fig. 2 was taken from the inner side. Note the improvement in the shape of the whole foot, in the position of the heel-bone, the absence of the head and neck of the astragalus, and the approximation of the scaphoid to front of the body of the astragalus.

was brought to me for treatment because he could not get any work on account of the deformity of the foot. He limped about with difficulty, and frequently fell, occasionally hurting himself. The left foot was in the extreme equinus position, with cavus and slight valgus. The heel was 4½ inches off the ground, all the weight being transmitted through the metatarsals to the balls of the toes, which were covered with corns and bunions (*vide* fig. 1). This attitude, which was fixed, made the left lower limb apparently longer than the right, and to lessen the disparity the left knee and hip were slightly flexed, and the spine was curved laterally. Really the left leg was an inch shorter than the right, as shown by measuring from the anterior superior spines to the tibial malleoli. The foot was small, and there were several corns upon its outer side and upon the toes, which were hyperextended at the metatarso-phalangeal joints as usual. The head of the astragalus was very prominent upon the front of the instep, and the internal malleolus projected to a lesser degree. The range of passive movement at the ankle was very small, and voluntary flexion was impossible. When the patient attempted to do this some of the tendons of the anterior tibial group of muscles could be seen and felt to move a little. The peroneal muscles were better, but weak. The superficial and deep calf muscles were greatly shortened. The knee-jerk was exaggerated; the plantar reflex was extensor ; no ankle-clonus could be obtained on account of the fixation of the ankle.

Diagnosis.—The character of the reflexes made it clear that the deformity must be due to a lesion affecting the upper neuron. The appearance was also characteristic, especially the extreme degree of equinus with slight valgus, intead of varus. In infantile paralysis there are more wasting, more vasomotor changes, more shortening of the limb, and the reflexes are absent, diminished, or unaltered, according to the severity and extent of spinal disease. Moreover, the absence of the reaction of degeneration served to exclude poliomyelitis. In Tooth's neuro-muscular paralysis the deformity is bilateral equino-varus, the reflexes are impaired, and there is wasting of the thenar and hypothenar muscles. I have recently seen a late case of

pseudo-hypertrophic muscular atrophy in which the deformities of the feet closely resembled those due to severe lateral sclerosis, secondary to cerebral lesions, but the knee-jerks are absent in this rare disease, and the patient raises himself up from the supine position in the characteristic way. Moreover, the scapular muscles are withered. The exact nature of the cerebral disease in my patient is uncertain; it was probably a cortical hæmorrhage or thrombosis affecting only the leg area. Such cases of monoplegia are not uncommon, and usually follow whooping-cough, measles, or influenza. A common form of the paralysis dates from birth, and is due to injuries to the head during delivery.

Treatment.—It was necessary to get the foot into a good shape and more natural position for many reasons : To enable the boy to get remunerative employment ; to distribute the pressure throughout the sole, and thus to cure the terrible corns before perforating ulcers could develop ; to secure an elastic gait with moveable ankle ; to do away with the flexion of the knee and hip, and the lateral curvature of the spine, and thus to avoid secondary osseous and articular changes. No apparatus could be invented which could confer these benefits. The patient was therefore admitted to Guy's Hospital under my care.

Operation.—After carefully cleansing the foot and leg, applying a tourniquet round the thigh, and administering a general anæsthetic, the following steps were taken in order :—

1. The tense plantar fascia was divided subcutaneously.

2. The ligaments below the medio-tarsal joint were divided subcutaneously through a puncture below the inner side of the joint. The fore part of the foot was forced upwards.

3. An incision four inches long was made in the groove, internal to and in front of the tendo-Achilles. This tendon was transfixed antero-posteriorly and cleft for five inches ; the outer half of it was cut off the os calcis, and the inner half was severed obliquely, five inches from this bone.

4. The tibialis posticus was divided. The ankle was forcibly flexed, but the foot would not come up sufficiently.

5. A longitudinal incision was made over the head of the astragalus. The extensor tendons were drawn aside. The astragalo-scaphoid joint was opened, and the head and neck of the astragalus were cleared. These were removed, an oblique section being made by means of a suitable osteotome. The section was made oblique in two senses, from above downwards and forwards, and from within outwards and forwards. In this way the equinus was corrected and the valgus was lessened. The overlapping ends of the heel tendon were then sewn together with fine catgut, the lengthening performed being four and a half inches. The dorsal ligaments attached to the scaphoid and astragalus were sutured and shortened, in order to bring the scaphoid close to the cut surface of the astragalus. The wounds were closed, and the foot covered with antiseptic dressings and firmly bandaged. The tourniquet was then removed, the leg and foot fixed in a back-splint and foot-piece, and well elevated. After the sutures had been removed, ten days later, passive movements were performed regularly, and active movements encouraged. Massage was also adopted. An open plaster splint was applied, and the patient discharged three weeks after the operation.

After six weeks he was provided with a surgical boot with three-quarter inch elevation, an external side steel, a T valgus strap and a toe-lifting spring. These he still wears during the day. At night he wears the plaster splint to prevent the toes dropping during sleep. At the present time, four months after operation, the patient walks well, and can move the ankle freely. It is very interesting and instructive to notice the great development of power in the anterior tibial group of muscles in the short time that they have been released from excessive tension, and provided with a range of movement. About a year from now the steel supports and the toe-lifting spring can be safely discarded. The slight elevation required to correct the permanent shortening can be concealed in the boot, so that it will be difficult for anyone to tell that there is anything wrong with the foot.

REMARKS.

In nearly all cases of talipes it is wise to use a tourniquet. This not only saves blood, but also time, and enables the surgeon to do far more accurate and clean work. There is no need to take the tourniquet off for the purpose of catching up the vessels before closing the wound. These peripheral vessels are easily controlled by means of firm bandaging over plenty of elastic dressings, provided that the pressure be applied before the tourniquet is removed, and the foot be kept elevated after the operation. This also lessens the pain.

As regards the order of the operative measures. It is easier to divide the plantar fascia and the plantar ligaments while the os calcis is fixed by the heel tendon. Moreover, it occasionally becomes clear that the latter need not be cut. It is not easy to divide the plantar ligaments until the arch is opened out by dividing all the tense bands of the plantar fascia.

Tendon lengthening is far more satisfactory than tenotomy when it is necessary to bring the heel down more than about one and a half inches; non-union with flail ankle may follow tenotomy for such cases. Moreover, the tendency to retraction with recurrence of the deformity is far greater after tenotomy than with tendon lengthening. Hence tenotomy has to be often repeated, whereas tendon lengthening, if properly done, is final, and it is less likely to be followed by wasting of the muscles. After repeated tenotomies I have noticed, upon exploration, that the lower part of the tendon is replaced by broad and thick sheets of adherent and contracted fibrous tissue.

In performing tendon lengthening it is best to adopt the simple method of cleaving the tendon into two halves. Usually, on account of varus, it is wise to leave the outer half of the tendon attached to the os calcis, and the reverse is true for valgus. In rare instances of pure equinus the tendon can be cleft from side to side. The ends are cut obliquely and sewn together without the least tension with fine catgut. In three weeks the lengthened tendon can be seen and felt to be satisfactorily joined and mobile also. The incision is always made in the furrow antero-internal to the tendon out of the reach of pressure. A flap must

not be raised because of the excessive tension upon the lower end of the wound when the heel is properly depressed.

Tendon lengthening is simpler and more satisfactory than section of the os calcis with displacement. Moreover, it has a wider range of usefulness. In many simple cases it is found to be unnecessary to divide the tibialis posticus, after the tendo-Achilles has been divided or lengthened. And in many instances resection of bone for the correction of the equinus proves to be unnecessary after dividing the soft parts in the order described. It may be wise to remove some bone, however, for correcting varus or valgus.

It is better to remove the head, or head and neck, of the astragalus than to resect a wedge including some of the astragalus and some of the scaphoid, because it is more efficient, and also because mobility of the mediotarsal joint is saved to some extent by preserving the articular cartilage of the scaphoid. By making the section of the astragalus oblique in suitable directions a variety of effects can be obtained with startling accuracy. In cases of equino-varus, the section is from without forwards and inwards as well as from above downwards and forwards. The remainder of the astragalus is thus used to prevent recurrence of deformity. The scaphoid swings round to articulate with the raw surface of the front and outer side of the astragalus and secured there by sutures shortening the dorsal ligaments. In my experience this method of correcting varus is more efficient than taking a wedge from the side of the body of the astragalus within the ankle joint. Moreover, the method that I have described does not interfere in the least degree with the mobility of the ankle, which is the most important one to preserve in the foot. The method which I have described is very easy, and the bone can be removed through a longitudinal incision running over the prominence of the bone. No tendons need be divided.

In cases of extreme varus, I also remove the fore part of the os calcis in a similar way. In such cases I make an elliptical incision running from the middle of the front of the ankle to the outer border of the foot, removing a good deal of skin which

would otherwise be redundant after removing the pieces of bone. When the wound is sutured the shortened skin and fasciæ help to correct the deformity. Through the same incision the tibialis anticus is transplanted to the cuboid for the correction of varus, or the peroneus tertius and the peroneus brevis to the scaphoid for valgus. Care is taken to fix the tendons to the periosteum, and not to submit them to excessive tension.

In the after-treatment it is essential to maintain the corrected position. Passive movements are usually carried out before the end of a week and voluntary actions are encouraged a little later. Massage and elevation are excellent safeguards against œdema. In the later after-treatment supporting instruments are usually needed for about a year. During this time muscles which have seemed to be paralysed from overstretching frequently regain much of their power, so that steel supports and toe-lifting springs can be discarded.

A CASE OF CONGENITAL DEFECT IN THE MUSCULATURE OF THE ABDOMINAL WALL.

By

W. M. MOLLISON, M.A., M.C.

CASES of congenital absence of the abdominal muscles are rare. In 1905 Garrod and Davies collected all the published cases and added two more, making a total of ten cases. Since then Bolton reported a case in the Clinical Society's Transactions in 1905, and in 1907 G. Hall added a further case, together with a description of a post-mortem examination of Bolton's case.

There appear to be no further cases recorded since then, so that the following case may perhaps be of some interest :—

Eric J., a boy nineteen months of age, was brought to the Out-patient department in August, 1908. His mother brought him at Dr. Clatworthy's suggestion, and not because the boy was in any way ill. Dr. Clatworthy had attended the boy for an attack of bronchitis a few weeks before, and had been struck by the singular appearance of the abdomen. The mother stated that the doctor who had delivered her had noticed the condition of the abdomen at the child's birth. The child was a healthy-looking boy, and could stand and run about like other children of his age. He had always been healthy except for the attack of bronchitis a few weeks previous to his attendance.

The abdomen presented a very striking appearance. The surface of the abdomen looked doughy, the skin was wrinkled, and there were two or three vertical furrows between the ensiform cartilage and the umbilicus; the umbilicus was much like the normal, only a little dragged out longitudinally. When the

child stood, the abdominal wall sagged downwards as it were resembling the condition seen in the worst cases of visceroptosis, and the lowest part hung so low as to partially hide the external genitals. The two photographs show the condition excellently. When the child lay down the abdomen was seen to bulge laterally; and when he cried this lateral bulging was most striking. In order to stand, the boy rolled over on to his abdomen. On palpating the abdomen no resistance was met with, even when the child cried, except in the upper part in the region of the attachment of the recti muscles to the thorax. There was almost complete absence of the abdominal muscles; on passing the hand into the loin, the quadratus lumborum was the first muscle met with. The wall was so lax that many details of the abdominal organs could be noticed. Coils of intestine could be felt; the spleen could be grasped in the left loin, and on the right side the liver margin was two inches below the costal margin. Neither the kidneys nor the ureters could be detected by palpation with any certainty; the bladder was not to be felt. The penis was well-developed, the prepuce was easily retracted, the scrotum was small, and the testicles were undescended, nor were they felt in the inguinal canal or iliac fossa. There was no sign of hernia.

Dr. Hertz kindly tested the abdominal wall electrically, but obtained no response in any part.

No other muscular defect was discovered in the whole body. The thorax was small, the costal margin projected somewhat, and a horizontal sulcus occupying the position of Harrison's sulcus was marked. There was no functional derangement as far as could be ascertained; the bowels acted regularly every day, and micturition was normal. Unfortunately these statements have not been able to be confirmed by observation, since the parents will not allow the child to be kept in hospital under observation even for twenty-four hours.

August, 1909.—The child has again been examined; he remains just as before in almost every respect. He is perfectly healthy, and still has no functional trouble of any kind. The abdomen presents very much the same features as it did a year ago. [The

A Case of Congenital Defect in the Musculature of the Abdominal Wall.

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photograph giving the lateral aspect was kindly taken for me by Mr. Hocking of the Evelina Hospital, in August, 1909.] There is now rather more resistance in the upper part of the abdomen; the recti appear to be present to a certain extent, and are represented by two bands attached to the thorax in the normal position, these bands fading away a short distance below the umbilicus; below this, the fingers can be sunk well into the abdomen without meeting any resistance whatever. The lateral parts of the abdominal wall are flaccid as before. The kidneys are not palpable, nor are the ureters, nor is the bladder.

Since the excellent and full paper by Garrod and Davies, a case was recorded by C. Bolton in the Clinical Society's Transactions, 1905. This was a case of a male three weeks old, in whom the lateral abdominal muscles were absent, but the recti present. The abdominal viscera were easily palpated. The bladder formed a pyriform tumour reaching almost to the umbilicus; there was a condition of phimosis; the testicles were undescended. In the flanks were coils seen which were thought might be ureters, since there was no resonance over them.

In 1907, G. Hall gave in the *Lancet* an account of the post-mortem examination on Bolton's case, and added a further case, which also died and was examined post-mortem. The post-mortem examination of Bolton's case showed that the recti muscles were present only above the umbilicus, and represented by aponeurotic bands below that; that the oblique muscles and transversalis were very slight in amount. The ureters were much dilated, and the left kidney was larger than the right, both showing fibrosis.

The second case was a child of two weeks old, a male, who had defect of the lateral abdominal muscles, but in whom the recti were present. The child had, in addition, an umbilical fistula discharging urine. At the post-mortem examination the recti were found present only in their upper parts; and the lateral abdominal muscles were only represented by a few fibres at their posterior attachments. The kidneys appeared normal, but the pelves were dilated, and the ureters were markedly dilated.

The following table gives the cases 1–12 in brief, arranged in chronological order :—

An abbreviated table of cases of congenital absence of the muscles of the abdominal wall.

(Taken in part from the table by Garrod and Davies.)

Observer.	Sex.	Age.	Muscles.	Bladder.	Kidneys and Ureters.	Testicles.
1. Frohlich 1839	M	Child.	P.M. Recti present; lateral wanting.	No mention.	No mention.	In scrotum.
2. Von Ammon 1842	M	Child.	Upper part of recti only present; lateral said to have developed at puberty.	No mention.	No mention.	No mention.
3. Henderson 1890	M	60 yrs.	Defect of lower part of lateral abdominal muscles and recti.	No mention.	No mention.	Undescended.
4. Parker 1895	M	New-born.	P.M. Recti slight; external and internal obliques slight.	Abdominal in position; wall ⅜in. thick.	Pelves and ureters dilated.	Undescended.
5. Guthrie 1896	M	9 wks.	P.M. Recti slightly present above; external obliques ditto.	Abdominal in position, fixed to umbilicus; hypertrophied.	Kidneys not large, but ureters enormous.	No mention.
6. Platt 1898	M	2 yrs.	Recti present; slight external and internal obliques.	Not felt.	No mention.	Undescended.
7. Osler 1901	M	6 yrs.	Costal attachments of recti only.	Abdominal, reached umbilicus.	No mention.	Undescended and not felt.
8. Stumme 1903	M	17 yrs.	Recti present above umbilicus; slight transversales.	Abdominal, very large; fixed to umbilicus.	Right kidney and ureter large; left ureter very large.	Undescended.
9. Batten 1905	M	9 mths.	Died. No P.M. No abdominal muscles.	Abdominal; fixed to umbilical scar.	No mention.	No mention.
10. Garrod & Davies 1905	M	8 wks.	P.M. No muscle in abdominal wall.	Abdominal; fixed to umbilical scar.	Right kidney and ureter small; left enlarged and ureter dilated below.	Undescended.
11. Bolton 1905	M	3 wks. (lived to 9 mths.)	P.M. Upper part of recti and small part of laterals posteriorly present.	Abdominal; fixed to umbilical scar.	Ureters dilated; left kidney > right.	Undescended.
12. G. Hall 1907	M	2 wks.	P.M. Upper part of recti, and a very small amount posteriorly of external and internal obliques and transversalis.	Hypertrophied and felt through abdominal wall.	Pelves dilated; kidneys not large; ureters much dilated.	Undescended.

The case of Eric J. resembles those previously recorded in many respects, the wrinkled skin, the bulging flanks, the small thorax with everted lower margin, the undescended testicles, the presence of a small part of the recti. But in one particular it differs greatly, and that is in the condition of the bladder. Of the eleven previous cases, in seven the bladder was abdominal or fœtal in position and generally fixed to the umbilical scar; in the other four, the bladder is either not mentioned (three cases) or is noted as not felt.

In the paper by Garrod and Davies, the various theories put forward by Stumme are discussed, and the authors conclude that the most probable theory is that the lack of muscle tissue is secondary to the condition of the bladder and ureters, which, in its turn, is determined by some obstruction during fœtal life.

This present case does not seem to bear out this theory, since the bladder is not abdominal in position, and there is nothing to suggest enlargement of the ureters.

It seems that all the cases can be divided into two groups, A and B.

In group A can be placed those cases that died before one year of age, cases 1, 4, 5, 9, 10, 11, 12. All these had some affection of the urinary tract (in case 1 there is no mention of bladder or ureters), and may well bear out the theory advanced by Stumme.

In group B come cases which survived at least two years, cases 2, 3, 6, 7, 8. Case 2 lived at least till sixteen years of age, case 8 was sixty, case 6 was two years, case 7 six years, and case 8 seventeen years old. Cases 2 and 3 are scarcely parallel with the rest, since in case 2 the muscles are said to have developed at puberty, and in case 3 only the lower parts of the muscles were wanting. This leaves cases 6, 7, and 8 to be considered. Two of these, 7 and 8, were patients of six and seventeen years respectively. The boy of six was ill and had great enlargement of the ureters and hypertrophy of the bladder, but had only begun to be ill at two years of age. The case of seventeen had large ureters and bladder.

Would not lack of development of the abdominal muscles account for hypertrophy of the bladder, and therefore dilatation of the ureters, as was suggested by Hall? In case 7 the costal elements of the recti only were present, and the boy at the age of six was very ill, and like to die shortly. In case 8 there were some fibres of the transversalis present, as well as the recti, above the umbilicus; this patient had lived for seventeen years, but his bladder and ureters were both large. Finally, case 6, a child of two years, had a slight amount of the external and internal oblique muscles and all the recti present; the bladder was not felt, and there is no mention of the kidneys or ureters, but it is probable they were not enlarged, since there is the special note on the bladder. This was only a slight case of defect, and doubtless the bladder did not work at great disadvantage.

The case of Eric J. fits into group B; he is now nearly three years of age, and has the upper part of the recti present; the bladder has been able so far to empty itself without any great difficulty, and has not hypertrophied sufficiently to be palpable; and there is no dilatation of the ureters noticeable. But it is most probable that at some future time the bladder will hypertrophy, and give rise to back-pressure results on the ureters and kidneys.

The theory of Stumme, that the condition of the urogenital tract gives rise secondarily to the muscular condition, does not seem to hold in this second group of cases. May not the cause and effect be interchanged? Granted a lack of development of the muscles, the enlargement of the bladder may follow.

CONCLUSIONS.

1. All cases of congenital defect in the musculature of the abdominal wall cannot be accounted for by the theory of intra-uterine obstruction to the urinary outflow.

2. Probably the lack of abdominal muscle gives rise to the hypertrophy of the bladder.

3. The greater the amount of muscle present in the abdominal wall the better the prognosis.

FOUR CASES OF GLANDERS IN THE HUMAN SUBJECT.

By

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AND

JOHN EYRE, M.D., M.S.

(From the Bacteriological Department.)

DURING the twenty years from 1887 to 1906, in England and Wales, only 85 deaths—an average of a little more than four a year—were registered as due to glanders. Although the disease is stated to be rare in man, it is probable that it is far more common than is implied by these figures, and we would suggest that the small number of returns is due to the difficulty of arriving at a correct diagnosis upon clinical observations alone. The symptoms of the infection are so varied, both in character and intensity, that certainty can only be attained by means of a bacteriological examination, and by bacteriological tests. If obscure or suspicious cases were more frequently investigated in this manner, we are convinced that the disease would be found with much greater frequency. Evidence in support of our contention is afforded by the occurrence of four cases of glanders, of which three proved fatal, in Guy's Hospital during the year 1908. In three of these cases a bacteriological examination established the diagnosis during life ; in the fourth, which died within forty-eight hours of admission, the disease was suspected during life, but confirmation of this suspicion was only obtained post-mortem. Brief details of these cases, in order of their admission, are here appended :—

CASE 1.—J. S., male, a horse dealer, æt. 40. For three months he had not been in his usual health, but had felt languid and

tired, with a persistent feeling of cold.   On January 30th, he was
taken suddenly ill.   He was thought to be suffering from pneu-
monia, and was admitted into Bright Ward under Dr. French on
January 31st.   The following day he became delirious and was
transferred to the strong room.   A localised swelling appeared
upon the forehead, which rapidly spread until the whole of the
scalp was involved, as described at the autopsy.   On February 3rd,
a diagnosis of glanders was made on the clinical appearances, and
confirmatory evidence was afforded by a positive sedimentation
reaction with B. mallei in a dilution of 1 : 250.   A papular and
pustular rash appeared, situated chiefly on the legs and arms,
with some larger collections of pus, both subcutaneous and inter-
muscular.   On February 5th, pus, collected from the lesion on the
forehead, yielded a growth of B. mallei, which, when inoculated
into the male guinea pig, provoked a typical glanders infection,
death taking place in forty-eight hours.   The patient died on
February 6th, after an illness of seven days.

At the autopsy, performed by Dr. Fawcett, the tissues over
the vault of the cranium from the root of the nose backwards
to the occipital protuberance were swollen from infiltration
with inflammatory products, and presented an irregular honey-
combed appearance where the tissues had broken down to form
ulcers and sinuses.   The bones of the skull were not invaded.
There were one or two small subcutaneous abscesses in the left
thigh.   Over the arms, and, to a less extent, the legs, were scattered
a few small papules and vesicles filled with opaque turbid fluid.
Scattered about in the substance of the right lung were small
solid nodules, varying in size from a pin's head to a cherry.   On
section of a large one it was seen to consist of a white firm
material with hæmorrhage into the lung substance around it.
Some to the naked eye looked like small infarcts ; others had the
appearance of grey "tubercles."   The left upper lobe was
occupied by a conglomeration of small cavities, the largest the
size of a walnut, thin walled, with a yellow lining membrane and
containing puriform fluid.   Around these cavities the lung was
in a condition of grey hepatisation.   In the left lower lobe were
many small tubercle-like nodules.   The fluid from one of these

cavities, inoculated into various tubes of nutrient media, gave rise to a growth of B. mallei, associated with the Staphylococcus aureus. The bronchial and mediastinal glands were enlarged, with a yellowish caseous-looking deposit, from which also B. mallei was obtained. On the left side of the glans penis was a hæmorrhagic infiltration with some loss of surface.

CASE 2.—W. C., æt. 32. male, horse-keeper, was admitted on March 11th, 1908, under Mr. Fagge into Samaritan Ward. He had been employed by the patient referred to as case 1, J. S. Six weeks before admission he had been kicked by a horse on the right calf. He continued to work, although with difficulty, because of the pain and swelling which had resulted. Four weeks from the time of injury he had to take to bed. On admission there was a small localised swelling in the muscles of the right calf, which caused great pain. His temperature was 101° F., the pulse 100. The swelling was regarded as a suppurating hæmatoma, and was incised soon after admission, when a small quantity of greyish-yellow viscid pus escaped. Cultivations therefrom gave a growth of B. xerosis only. The wound slowly healed, but there was no improvement in the general condition. A history of malaria acquired in India several years previously led to a search for malarial parasites, but this yielded negative results. Cultivations made with blood collected from the median basillic vein remained sterile. B. mallei was, however, agglutinated by the patient's serum in dilutions up to 1 : 200, while B. typhosus was not agglutinated even by 1 : 10 dilutions. Collections of pus, similar in appearance to that of the original abscess, formed in the subcutaneous tissues and in the muscles, and were incised at long intervals. In each case the contents were submitted to bacteriological examination. Thus :—

April 4th. Pus from a costal abscess contained Strepto-
coccus longus.

May 5th. Pus from an abscess over right hip-joint con-
tained B. mallei in pure culture.

July 7th. Pus from an abscess of left leg contained
Staphylococcus aureus.

Aug. 21st. Pus from an abscess of foot contained B. mallei.

All these abscesses were characterised by the same chronicity as was shown by the original abscess in the right leg. In addition, on March 30th the right elbow-joint became painful, and was drained on April 3rd, and on June 1st a swelling formed at the root of the nose, which was opened to allow pus to escape on July 7th. Examination of the blood on September 30th showed that specific agglutinins were present in lesser amounts than previously. Dilution 1 : 80 of the serum now failed to sediment B. mallei, though 1 : 40 dilution still gave a fairly strong reaction. A week later 1 : 50 dilution reacted well, but 1 : 80 dilution was still negative. A vaccine was prepared in the ordinary way from the glanders bacillus isolated from the pus from the foot abscess with a view to treatment, but as injections of 100,000 millions of the dead bacilli into a guinea-pig of 500 gram. weight caused the death of the experimental animal within three days from acute toxæmia, a further supply of vaccine was prepared, and digested for three days with pepsin and hydrochloric acid, the acid neutralised and a dose estimated to contain 10,000,000 bacilli tested on guinea-pigs. As the dose had no effect upon the animals beyond provoking the formation of specific agglutinins, a dose of (estimated) 100,000 bacilli was injected into the patient. This dose, however, provoked a typical mallein reaction, both local and general, and the patient, who had been inoculated against typhoid in India, absolutely refused to undergo further treatment, and on October 28th was discharged at his own request. He still had slight pyrexia. Pus was escaping from the incision at the root of the nose, and from the wound which had been made in the left leg.

CASE 3.—P. G., æt. 28, a horse-keeper, was admitted under Mr. Lane into Lazarus ward on August 17th, suffering from pyrexia and pains in the joints. Two years before he had admittedly been in contact with a glandered horse, but until July 30th he had been in perfect health. On that day he had been struck over the right scapula by the shaft of a cart. The next day he called in a doctor, who found the place swollen and applied iodine. On August 10th the swelling was incised without result. On admission on August 17th the patient was very ill, listless, and apathetic, with

a high temperature and feeble pulse. His tongue and mouth were in a very foul condition, so foul indeed as to suggest the possibility that the arthritis was of that toxic variety sometimes associated with pyorrhœa alveolaris. On August 20th, and again on August 25th, clear fluid was withdrawn from the left elbow-joint, which had become swollen and painful. Cultivations remained sterile on both occasions. On September 8th, the patient's blood serum, when tested against B. mallei gave a positive sedimentation reaction in dilutions of 1 : 250 and 1 : 500, and a diagnosis of glanders was made. He grew gradually weaker, and when *in extremis* on September 11th (about 5 p.m.) a small dose of B. mallei vaccine was administered, but the patient died exhausted the following morning.

At the autopsy there was no sign of external injury. The right scapular region and the left elbow-joint were examined and nothing abnormal was detected. There were no subcutaneous or intermuscular abscesses, and no papular or vesicular rash. On the posterior aspect of the thyroid cartilage, at the lower border of the left wing of the cartilage, there was situated a group of small nodules, three or four in number, the largest about the size of a pea. They were hard and fibrous to the touch. On section each had a yellow caseating centre. There was no active ulceration and no hæmorrhage into the mucous membrane around them. On section of the cartilage the nodules were seen to be extending into its substance. Caseous material from the interior of these nodules gave rise to a pure growth of B. mallei. At the anterior border of the middle lobe of the right lung was a small nodule, which on section contained a small quantity of grey gelatinous pus. It was surrounded by a hæmorrhagic zone, the whole being about the size of a cherry. Cultivations from the gelatinous pus yielded a pure growth of B. mallei; some of the pus which was injected into the peritoneal cavity of a guinea-pig caused death in forty-eight hours, associated with a typical Strauss' reaction. Except for numerous petechiæ scattered under the pleura, these were the only abnormal appearances found post-mortem. Sections of

the nodules from the larynx showed a central caseating mass, surrounded by dense fibrous tissue. No giant cells were seen.

Spleen.—Cultivations from the spleen pulp gave a growth of B. mallei associated with B. pyocyaneus. A subcultivation of the B. mallei injected into a male guinea-pig caused death in twenty-four hours, the typical purulent inflammation of the tunica vaginalis and testicle being observed post-mortem.

CASE 4.—S. C., male, æt. 20, a clerk, who was not known to have come in contact with horses, was admitted under Dr. Hale White into Addison ward on October 31st. His illness had begun on September 24th with fainting attacks, a feeling of great weakness and vomiting. On September 27th he developed a very painful swelling of the left clavicle, which subsided. On October 12th a similar painful swelling appeared on the right tibia. At this time he was not apparently seriously ill, and the appearance of the swelling on the tibia, with the subsidence of that on the clavicle, was such as to suggest a diagnosis of syphilis. On October 31st, quite suddenly, he became much worse, and was admitted. A huge boggy swelling appeared suddenly on the frontal region, completely closing one eye. He was delirious, and obviously dying. On November 1st, a pustular rash appeared on the body. He died early the following morning.

At the autopsy pustules were scattered over the neck, arms, and legs. Only two or three were present on the trunk. Each contained a little glairy pus, of a grey rather than a yellow colour, and cultivations therefrom gave a growth of B. mallei. Pus, of the same colour and appearance, exuded from the subcutaneous tissue over the right internal malleolus and from the tendon sheaths in the neighbourhood. Cultivations showed the presence of B. mallei. Some of the pus inoculated into a guinea-pig caused death in three days, with positive Strauss' reaction. Pus obtained from the left ankle-joint also contained B. mallei. The tissues of the scalp over the frontal bone were infiltrated and undermined. The bone was not affected. The left clavicle was perfectly normal. There was a single necrotic area, the size of a cherry, at the anterior border of the right lung.

A small abscess was found in the globus major of the left epididymis. There was a superficial abrasion, covered with grey pus and without induration, on the glans penis. The pus from this situation contained B. mallei associated with staphylococcus albus. Microscopical examination of the deposit in the epididymis showed it to consist of a central necrotic mass with many pus cells surrounded by a zone of congestion.

Spleen.—Cultivations from the spleen pulp remained sterile. Serum from the heart blood, collected post-mortem, gave a positive sedimentation reaction when tested against B. mallei in dilutions up to 1 : 200.

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Mode of infection.—Three of the cases had admittedly been in close and constant association with horses. The fourth case was believed to have had no connection with horses at all. In none was the infection obviously direct, either by contamination of a wound or by inhalation of infected secretion. In the first three cases, the history definitely suggests that the infection was of some standing. Case 1 had had vague symptoms of ill-health for at least three months before his sudden seizure ; case 2, who was in the employ of case 1, was presumably infected from the same source, while case 3 was known to have been in association with a glandered horse which had been slaughtered two years before. That in case 3 the acute symptoms should have followed directly upon an injury to the shoulder, after the lapse of so long a time, is comparable with what is not infrequently found in tubercle, where trauma apparently acts as the exciting cause of a tuberculous lesion. In case 2, similarly, the first symptoms of ill-health followed upon a kick from a horse, and the earliest obvious lesion presented itself as a hæmatoma undergoing a somewhat tardy suppuration. Yet in only one of these three cases could any history of previous chronic ill-health be obtained. In two, the disease apparently had been truly " latent." Moreover, the post-mortem appearances, fibrosis, caseation, etc., were in accord with the supposition that the infection in each case was of old standing. On the other hand, in the fourth case there was no hint of previous chronic infection, and, in accordance with this,

the post-mortem appearances were acute and recent, showing no trace of repair.

Diagnosis.—Clinical.   In case 1, before the importance of the history of indefinite illness for three months was realised, a diagnosis of pneumonia had been made, not unnaturally, in view of the post-mortem appearances of the lungs.   The terminal symptoms, however, were characteristic, as they also were in case 4.   In both the papular and pustular eruption bore a super- ficial resemblance to the rash of small-pox.   In more than one recorded case this mistake has been made, and the patient has been admitted to a fever hospital.   In cases 1 and 4, however, the distribution of the rash, most marked upon the extremities, its late appearance after many days of illness, and the simultaneous presence of subcutaneous collections of pus, prevented the mistake.   In no case was the disease confused with tubercle, but case 4 presented at one time symptoms which were thought to be due to another of the infective granulomata, namely, syphilis. He was not at first very ill, and the rapid and complete sub- sidence of the clavicular swelling suggested that it was a syphilitic node.   At the time, however, the extreme tenderness and great pain were regarded by Dr. Hale White as evidence against this diagnosis.   The same rapid subsidence of the swelling, and the same acute pain, were noted and recorded by Mr. Lane in the swelling over the scapula in case 3.   In neither case did the bone show any evidence of disease when examined post-mortem. Moreover, in both an ulcerated sore on the glans penis was found post-mortem, although this appeared so late that it could hardly be said to have in any way obscured the diagnosis.   Cases 2 and 3 both presented the usual symptoms of a chronic blood infection, prostration, pyrexia, sweating, foul mouth and tongue.   They differed in that, while in case 2 abscess after abscess was opened and drained, with little relief of the general symptoms, in case 3 no abscesses were found either post-mortem or during life.   The distribution of the lesions corresponded very closely with what has been met with in other cases.   The root of the nose and frontal region was the seat of suppuration in three cases, and, as has been noted, the glans penis was involved in two.   In all the

cases upon which a post-mortem was performed, the respiratory tract and lungs were involved, and the appearances of the lesions in these situations were such as to lead us to regard them as the primary infective foci. The only other visceral lesion was found in the epididymis of case 4. The extent of the lesions post-mortem bore no relation to the intensity of the toxæmia. Case 3 died exhausted from pyrexia and sleeplessness, and yet the only post-mortem lesions found were two small apparently chronic nodules each less than a shilling piece in size. In case 4 all the disease was recent; in case 1, some of the foci were recent, others of long standing.

Diagnosis—Bacteriological. The colour and consistency of the pus, both from the subcutaneous abscesses and from the cutaneous vesicles, was characteristic. It was grey rather than yellow in colour, viscid and glairy. In no instance was there suppuration found in a joint post-mortem, thus contrasting with what is found in pyæmia generally. In two of the cases, 1 and 2, microscopical examination of films prepared directly from the pus failed to show the glanders bacillus in the majority of the instances in which it was examined. An organism resembling B. xerosis (a common skin saprophyte, and staining by Gram's method) staphylococci, and on one occasion streptococci, were all that could be detected microscopically. In case 2 in one instance only was a Gram negative bacillus resembling glanders bacillus detected in the pus, although a total number of eight specimens were examined. In case 4, however, the glanders bacillus was recognised in film preparations direct from the pus obtained from the cutaneous pustules and from all the various lesions examined. It was noted in the spleen pulp, although in very small numbers. In case 3, B. mallei was seen microscopically in pus from all the lesions observed post-mortem, but was not found microscopically in the spleen pulp.

Serum reaction. — The sedimentation reaction of the blood serum, when tested against B. mallei in various dilutions, was very marked in all four cases. In case 1 it was obtained in dilutions up to 1 : 250. Case 2, when first seen, gave the reaction in dilutions up to 1 : 200, but as the case progressed the amount

of specific agglutinin present in the blood diminished, so that after the patient had been under observation some three months the titre of the serum had fallen to 1 : 80. In case 3 the reaction was obtained in dilutions up to 1 : 500, and in case 4 blood obtained post-mortem gave a reaction up to 1 : 200. It will thus be seen that the blood reaction in each instance was definite and absolute. In two instances the blood was tested against B. typhosus also, but no reaction could be obtained even with such low dilutions as 1 : 10. The diagnostic value of this serum reaction is of great importance, and in no instance, where normal blood serum has been tested against B. mallei, have we been able to detect a sedimentation reaction in higher dilutions than 1 : 5, and even in that dilution the reaction was by no means conclusive.

Cultural characters.—B. mallei was isolated from each of these cases ; in case 1, both before death and at the post-mortem. In case 2 the organism was also isolated, but only after many failures ; pus from the exceedingly chronic lesions in this case apparently containing the organism in very small numbers only. In case 3 the organism was not isolated until after death. The same holds good for case 4. The strain of B. mallei isolated from each of these four cases was precisely similar, and corresponded exactly to the typical glanders bacillus.

Inoculation experiments.—In each instance the glanders bacillus isolated from the patient was inoculated into a full-grown male guinea-pig ; and in contradistinction to the type of glanders bacillus usually isolated from glanders in the horse, where the virulence is usually low, the bacillus here found (in man) was in every instance of a fairly high virulence. A small quantity of an agar culture (1 loopful) injected into the peritoneal cavity of the guinea-pig caused death always within three days, with the characteristic inflammation of the tunica vaginalis, which goes by the name of Strauss' reaction. In two cases, 3 and 4, the injection of 0·1 c.c. of the pus from one or other of the lesions produced a similar effect.

THE PATHOLOGY OF PAROXYSMAL HÆMOGLOBINURIA: A CRITICAL REVIEW.

By

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(Thesis for the Degree of M.D. in the University of Cambridge.)

EXPERIMENTAL evidence has shown that the injection of hæmoglobin into the circulating blood, or the setting free of hæmoglobin by the solution of red corpuscles, leads to a great increase of bilirubin. The iron-containing part of the hæmatin is split off and retained, probably in the liver. It has been stated by Hayem that the serum which separates from blood always contains free hæmoglobin—that there exists, in other words, a physiological hæmoglobinæmia. Schäfer was, however, unable to prove this experimentally. Whether it be true or not, these experiments show that hæmoglobinæmia, however produced, results first in an increase of bilirubin and so in polycholia.

The power of the liver to cope with a pathological or experimental hæmoglobinæmia is great. But when the quantity of free hæmoglobin in the serum passes a certain point, use is made of a more direct means of exit, and the result is hæmoglobinuria. Ponfick and Stadelmann, independently, have shown that this does not occur until the amount of free

hæmoglobin reaches one-sixtieth of the total hæmoglobin content
of the body.   Camus more recently has shown that a destruction
of red cells equivalent to one fifty-seventh of the total hæmoglobin
of the body may take place without any appearance of the
pigment in the urine.   The spleen and marrow, he states, come
to the help of the liver, and the hæmoglobin is there stored in
the form of hæmosiderin.   If the products be thus stored,
regeneration of the blood is more rapid than would be the case
if the pigment were entirely lost.

It is obvious, therefore, that while, in the light of our present
knowledge, hæmoglobinuria is impossible without a preceding
hæmoglobinæmia, the degree of hæmoglobinæmia required to
produce hæmoglobinuria must always be very large.   In any
investigation of the pathology of paroxysmal hæmoglobinuria,
it is necessary to consider first the nature of hæmolysis in
general and the various factors which may cause it.

1. In the first place, hæmolysis may be due to purely physical
causes.   Trituration of red corpuscles with sand will cause their
disintegration.   The addition of distilled water or the alternate
freezing and thawing of blood will also cause hæmolysis.

2. Some chemical substances such as alcohol, urea, ammonium
chloride, and glycerine penetrate the red cells and disorganize
them.   Injection of 10 per cent. solutions of urea will cause
intravascular hæmolysis, but if by the addition of sodium chloride
this solution is made isotonic with the blood plasma, no
hæmolysis will occur.

Saponin and some other glucosides are intensely hæmolytic.
It is believed that this is due to the action of these glucosides
upon the cholesterin of the corpuscle, and it has been shown by
Ransom that cholesterin can protect the corpuscles from saponin.
The action of these substances occurs in three steps—first the
envelope is affected, next the pigment escapes, and, finally, the
electrolytes pass out.

3. Hæmolysis may be produced by the action of toxic
phytalbumoses, such as ricin and abrin, bacterial toxins such as
tetanolysin, and by some constituents of snake venom.

4. Certain drugs may cause hæmolysis, notably chlorate of potash, nitrites, phenylhydroxylamine, and bodies of the phenacetin group.

5. It has for some time been well known that the serum of one animal may be hæmolytic to an animal of another species. Transfusion of sheep's blood into the vessels of a man causes fever and hæmoglobinuria, and Landois showed that this was due to a specific globulicidal action. The serum of a dog is hæmolytic to rabbits, and that of a horse is hæmolytic to guinea-pigs.

Belfanti and Carbone found that, on injecting the blood corpuscles of a rabbit into a horse, the serum of the horse became toxic to the rabbit. Bordet and Ehrlich and Morgenroth made further investigations, and, by injecting defibrinated ox-blood into rabbits, obtained a serum hæmolytic to oxen.

History.

Paroxysmal hæmoglobinuria was first observed by Charles Stewart in 1794. Rayer, in his "Treatise on Diseases of the Kidneys," published in 1841, gives a vague reference to the disease. Dressler, in 1854, published an account of an "Intermittent Albuminuria and Chromaturia," the first satisfactory description of the disease. He pointed out that the urine contained only a brown amorphous pigment, and that no blood corpuscles were to be found in it.

During the following decade, cases were described in England by Harley, Dickinson, Gull, Hassall, Pavy, and others. Hassall recognized that the pigment found in the urine was hæmoglobin, and further that the disease was almost exclusively a cold-weather ailment. He accordingly named it "winter hæmaturia." Dickinson was of opinion that the disease originated in the kidneys.

With the introduction of refined methods of investigation and the use of the spectroscope the name "hæmoglobinuria" was definitely adopted. The title "Paroxysmal Hæmoglobinuria" was first suggested by Secchi. Ringer, in 1868, remarked that not only cold, but also a number of other causes might give rise to this condition. Greenhow attempted to trace resemblances

between paroxysmal hæmoglobinuria and malaria. Wiltshire ascribed the condition to an autogenetic intoxication, and suggested the name " paroxysmal hæmolysis."

In 1881 Fleischer pointed out that severe exertion might cause paroxysms. In Strubing's patient, attacks were said to follow alcoholic bouts and excitement. Kast described a case in which prolonged exertion caused attacks, while cold was ineffectual. Prior found that both cold and exertion could produce paroxysms.

Many of the early hypotheses as to the causation of the disease were fanciful, and of purely historical interest. Some writers were of opinion that it was due to disease of the kidneys, nephritis or congestion. Pavy believed that a vaso-motor disturbance, acting upon the blood, caused congestion of the viscera, especially the kidneys.· von Popper considered that the disease was due to a vaso-motor neurosis.

The relation between paroxysmal hæmoglobinuria and malaria was in the early days a subject of much speculation, and it is possible that some of these earlier cases were really malarial hæmoglobinuria, and that the diagnosis of paroxysmal hæmoglobinuria was not justified. The occurrence, in many cases, of syphilis as an antecedent was not recognized until later.

The credit of the discovery of the disease thus rests with Dressler, and the first description in English is by Harley. In the period following this, as has been seen, many cases were recorded in England and elsewhere. The first philosophical study of the disease was carried out by Murri of Bologna. Mesnet published the first French account of the disease. Chvostek, in 1894, made an exhaustive analysis of the literature of the subject, and investigated a number of cases under his care. More recently, the work of Eason in this country, and that of Donath in Germany, have broken entirely fresh ground and added considerably to our knowledge.

NOTES UPON CASES.

Paroxysmal hæmoglobinuria may occur at any age, but is rarely found in patients above the age of fifty. It is as common

in children as it is in adults. The majority of the patients are males.

A hæmoglobinuric patient is typically pale and anæmic, usually weak and ill-nourished. This is, however, by no means always true. Some patients, though pale, are powerful and well-built, and some are healthy-looking people with good complexions.

There are, in all cases, well-marked prodromal symptoms, which enable the patient to foretell an attack. These vary in different patients, but the most frequent are yawning, pains in the back spreading to the limbs, cramps, cyanosis, abdominal pain, and, less frequently, shortness of breath. There is, at the same time, a shivering and a feeling of cold that prompts the patient to seek the warmest place within reach. In an hour or two, the patient passes dark-red or dark-brown urine, which on examination shows the spectrum of oxyhæmoglobin or methæmoglobin.

At the beginning of last year there were in Guy's Hospital three cases of paroxysmal hæmoglobinuria, but unfortunately only one patient was content to stay under observation. He stayed in the hospital five weeks, and still comes from time to time to report. He is a man aged 36, of medium height, pale and anæmic, but well-built. He has never been abroad. He is a casual labourer, finding employment principally in docks and river-side factories. Twelve years ago he was a pugilist of some note.

In 1895 he had syphilis, followed by slight secondary symptoms. In 1897 he had pneumonia. He is not a person of great intelligence, and it was difficult to obtain an exact history of the occurrence of hæmoglobinuria. In 1900, while at work, he started shivering and became dizzy and had to stop work, but his urine was not altered. In the year following, while at work in dry dock, he had a similar attack, but this time it was followed by the passage of " black urine." Since then, he has been subject to attacks every winter. In the cold summer of 1907 he also had attacks. He volunteered a statement that when he felt cold exertion did not produce warmth, but rather

made him colder and colder until a paroxysm supervened.   This
has also been noticed by Eason.

In April, 1904, he was admitted into Guy's Hospital for
" hæmoglobinuria and rigors."   There were severe gastro-
intestinal symptoms, such as diarrhœa and vomiting.   No urinary
casts were found, nor were there physical signs of heart-disease.
Probably these gastro-intestinal symptoms are due to polycholia,
which, as previously stated, is a logical antecedent of hæmoglo-
binuria.   Although anæmic, and sometimes " lemon-tinted," it is
not stated in any of the reports that W. E. was jaundiced.

In the autumn of 1905 he was again admitted into the hospital
in very much the same condition.   No physical signs of heart-
disease were found.

After his discharge from the hospital on this occasion, he got
into regular employment.   In spite of occasional paroxysms, he
did not seek medical advice, as he was unwilling to run the risk
of losing his work.   In the beginning of 1908, however, he found
that his health in other respects was unsatisfactory, and, on
February 25, he came up to the hospital and was admitted—in
the height of a paroxysm.

In the receiving-room he presented many of the symptoms
premonitory of an attack, such as shivering, yawning, pains in
the back, and cramps.   Half an hour after admission he passed
dark-brown urine, and it was ascertained by means of the
spectroscope that methæmoglobin was present.

It was found that he had aortic disease : systolic and diastolic
bruits were heard in the aortic area, and a Flint's bruit was
heard over the impulse.   The lungs were emphysematous.   The
liver was not enlarged.   An examination of the nervous system
showed nothing abnormal : in this respect a great change was
found six months later.   This physical examination was made on
the day after admission, after the termination of the paroxysm.

EXPERIMENTS.

W. E. remained in the hospital for five weeks, and during this
time had six paroxysms.   For the greater part of the time he was
not confined to bed, but permitted to walk in the grounds when

the weather was favourable. When the day was sufficiently cold, a paroxysm could readily be induced by sending him into the open air : cold baths and such drastic measures were unnecessary.

Experiments upon the blood *in vitro* were performed with a view to finding whether a specific hæmolysin was present, and to an investigation of the scope and mode of action of such a hæmolysin, should its presence be proved. I can claim no originality for this research, as Eason has been over the ground very thoroughly, and I have consequently been able to do little more than confirm his observations.

The apparatus used consisted of a rack of small sterilized test-tubes plugged with cotton-wool, an incubator at 37°C., and a receptacle filled with ice-water ; a centrifuge and two saline solutions. These solutions were—(1) a solution of potassium oxalate, 0·25 per cent. in a 0·85 per cent. sodium chloride solution, hereinafter referred to as the oxalate solution, and (2) a 0·85 per cent. sodium chloride solution, referred to later as the saline solution.

Blood was obtained from the finger or from the lobe of the ear. The first series of experiments was performed with blood obtained during an interval between two paroxysms.

(1) Blood from W. E. was mixed with twice its volume of oxalate solution, and divided into two portions. The first portion was put into ice-water for half an hour, and then into the incubator for twelve hours. The second portion was put into the incubator for twelve hours. Hæmolysis occurred in the first tube, but not in the second. Similar control experiments were done with my own blood, and hæmolysis did not occur in either tube.

Similar experiments were performed on the following day with this modification. It was a cold day (42° F.) and the patient went out into the cold air. A test-tube containing the oxalated blood was also put in the open and subsequently—after warming—hæmolysis took place *in vitro*. The patient also had a paroxysm. Thus the same conditions of temperature produced hæmolysis simultaneously *in vivo* and *in vitro*.

· Another specimen of oxalated blood was put in the ice-water for half an hour, and then left in the test-tube rack all night, and not in the incubator. No hæmolysis took place, until after a subsequent warming in the incubator. · This shows that a cold stage and a warm stage are both necessary for the production of hæmolysis.

On another day, another portion of blood was taken and mixed with oxalate solution, as above. It was divided into two parts, A and B. A was put into ice-water for half an hour and then centrifugalized. The serum (a) was drawn off. The corpuscles (b) were washed free of serum in the following way. Saline solution was added until the original bulk of liquid was equalled. The mixture was then shaken and again centrifugalized. The clear fluid was poured off and more saline solution was added. The mixture was again shaken and centrifugalized. The clear fluid was then poured away, and the process repeated once more. By this means the last traces of serum were washed away.

The second portion, B, was not put into ice-water, but centrifugalized at once. Serum (c) and corpuscles (d) were separated and washed as above.

1. a (iced serum) and b (iced corpuscles) were added together, and put in the incubator for twelve hours. Considerable hæmolysis followed.

2. a (iced serum) and d (un-iced corpuscles) were added together, put into ice-water for half an hour and then incubated. No hæmolysis followed.

3. c (un-iced serum) and b (iced corpuscles) were added together and incubated for twelve hours. Hæmolysis followed.

4. b (iced corpuscles) with a suitable bulk of saline solution was put into the incubator for twelve hours with no hæmolysis.

The first and last of these experiments, (1) and (4), show that, although the first stage of hæmolysis is effected during the cold stage, yet corpuscles and serum must remain in contact during the warm stage if hæmolysis is to follow. That is to say, that during the cold stage the corpuscles are acted upon in such

a way as to render them vulnerable to the action of some component of the serum in the warm stage.

The second experiment (2) was uncertain in its results On this occasion I found that no hæmolysis occurred. On repeating the experiment on other days, at one time there was a slight degree of hæmolysis, and at another time hæmolysis was quite marked. The explanation of this may be that during exposure to cold, the erythrocytes rob the serum of one of its components. This component renders them vulnerable to that other component of the serum, which in the subsequent warm stage completes the process of hæmolysis. After exposure to cold in company of the corpuscles, the serum is wholly or in part robbed of one of its components. If no trace of this component is left, the serum becomes inactive by exhaustion and, if added to red corpuscles, will not produce hæmolysis when incubated, unless the corpuscles themselves have, from a previous icing, had the opportunity of linking themselves to the missing component. If on the other hand—this is the more common condition— this component has not been completely abstracted, then the experiment will end in hæmolysis. The degree of hæmolysis possibly bears a rough proportion to the activity of the serum.

The third experiment (3) shows that for the completion of— to use a loose term—the warm stage of hæmolysis, it is not necessary for the component of the serum which acts during this stage itself to have been exposed to cold.

If the terminology of the immunity hypothesis be applied to these experiments, they may be interpreted in the following way. In paroxysmal hæmoglobinuria there exists in the serum a specific hæmolysin. The hæmolysin is made up of two constituents, amboceptor (intermediary body) and cytase (alexine or complement). When the blood is exposed to a low temperature the amboceptor becomes linked to the corpuscle. The cytase is active only at the body-temperature and cannot act upon a corpuscle alone, but only upon the corpuscle + amboceptor group. Therefore, when in an incubator the blood is kept at the appropriate temperature a destructive combination of the three bodies, corpuscle, amboceptor, and cytase, occurs.

During another interparoxysmal period, a third series of experiments was performed. A portion of blood from W. E. was mixed with oxalate solution, and divided into two portions, *A* and *B*. The first portion, *A*, was put into ice-water for half an hour and then centrifugalized into (*a*) serum and (*b*) corpuscles as before. In the case of *B*, the ice-water stages were omitted, but (*c*) serum and (*d*) corpuscles were similarly separated. A specimen of normal blood, *C*, was taken from my own finger and divided by the centrifuge into serum (*e*) and corpuscles (*f*).

1. *a* (iced serum of W. E.) was exposed to a temperature of 56° C. for half an hour. It was then added to *b* (iced corpuscles of W. E.) and put into the incubator for twelve hours. No hæmolysis occurred. Then *e* (serum of H. M.) was added and the tube was again put into the incubator for twelve hours. Hæmolysis ensued.

2. *c* (un-iced serum of W. E.) was exposed to a temperature of 56° C. for half an hour. It was then added to *d* (un-iced corpuscles of W. E.), and the tube was put into ice-water for half an hour, and then incubated for twelve hours. No hæmolysis occurred. *e* (serum of H. M.) was added, and the incubator stage repeated. Hæmolysis then occurred.

3. *c* (serum of W. E.) and *f* (corpuscles of H. M.) were added together, put into ice-water for half an hour, and then into the incubator for twelve hours. Hæmolysis occurred.

4. *e* (serum of H. M.) and *d* (un-iced corpuscles of W.E.) were together put into ice-water, and then incubated for twelve hours. No hæmolysis took place.

The first and second experiments of this series show that the cytase is destroyed and rendered inactive by exposure to a temperature of 56° C. for half an hour. But experiment (2) shows that this temperature does not destroy the amboceptor. Further, the two experiments show that the cytase is not peculiar to the blood of hæmoglobinurics, but occurs also in the serum of normal blood. The last experiment (4) shows that the amboceptor does not occur in normal blood, but only in that of affected persons. The third experiment (3) shows that this hæmolysin can destroy normal corpuscles, and consequently

that it is not necessary to assume that there is any diminished power of resistance in the corpuscles of the hæmoglobinuric.

The conclusions to be drawn from these three series of experiments are as follows. There exists in the serum of hæmoglobinuric patients a specific hæmolysin, consisting of two portions, amboceptor and cytase. The cytase is destroyed at a temperature of 56° C., but the amboceptor resists this temperature. The cytase is a constituent not only of hæmolytic, but also of normal serum, but the amboceptor occurs only in the serum of affected persons. This specific hæmolysin is isolytic as well as autolytic; that is to say, it is capable of producing hæmolysis if added to normal blood. It is not therefore necessary to assume any specific vulnerability in the corpuscles of the hæmoglobinuric.

During the time that W. E. spent in the hospital, six paroxysms occurred, and I was able to perform a few experiments on the process of hæmolysis *in vitro* with blood obtained during one or other of these paroxysms.

Blood was obtained from W. E. at different stages of the paroxysm, and allowed to clot in a small hermetically-sealed tube. In a severe paroxysm it was found that a pink tinge could be observed in the serum an hour after the first exposure to cold, and this persisted for perhaps an hour to two hours after the first appearance of hæmoglobinuria. In less severe paroxysms, the pink tinge of the serum disappeared before any hæmoglobin appeared in the urine.

In a severe paroxysm, but before the appearance of hæmo-globinuria, blood was obtained from W. E. and mixed with twice its volume of oxalate solution. It was placed in the incubator for twelve hours, and hæmolysis occurred. Another sample of blood was taken at the same time as that required in the foregoing experiment, and allowed to clot in a tube. The serum showed no signs of free hæmoglobin. The corpuscles had probably united with the amboceptor *in vivo*, as no cold stage was required *in vitro* to produce hæmolysis.

Eason obtained blood from one of his patients at the beginning of a sharp paroxysm, mixed it with an equal part of oxalate

solution, and centrifugalized quickly.   There was no apparent hæmolysis.   The corpuscles were washed in the manner described above.   He then treated some of his own blood similarly, and thus obtained a normal oxalated serum.   This normal serum was then added to the corpuscles, and incubated for twelve hours.   Hæmolysis occurred, showing that union of corpuscles and amboceptor had occurred in the vessels of the patient, and that the addition of cytase was sufficient to produce hæmolysis on incubating.

Further, he added the serum of the patient, obtained at the same time as the foregoing experiment, to his own normal washed blood corpuscles.   No hæmolysis occurred after twenty-four hours in the incubator.   But another similar preparation was placed in ice-water for half an hour, and then incubated.   In this case hæmolysis did occur, showing that, although the serum had given up amboceptors to the corpuscles, as shown in the previous experiments, yet it retained a sufficiency of amboceptors to produce further hæmolysis on a return to suitable temperature conditions.   This experiment suggested to Eason the following hypothesis :   the limitation of the paroxysm may not be determined by the using up of the intermediary bodies (ambo-ceptors), nor even by the formation of anti-intermediary bodies but simply by a restoration of the body to temperature conditions which do not further favour the anchoring of intermediary bodies to the cells.

Eason performed a large number of experiments with serum obtained from his patient by means of blisters, and found that the blister serum was hæmolytic under the same conditions as the blood serum.   On one occasion I applied a blister to W. E. in the hope of performing experiments with his blister serum, but he resented the process so much that I was obliged to abandon them.

These experiments all lead to the conclusion that there is, in the blood of hæmoglobinurics, a potential hæmolysin, called into activity by those influences which have been already referred to as the causes of paroxysms.   Of these, cold is the most prominent.   This hæmolysin is composed of amboceptor, the

characteristic element, and cytase, which occurs also in normal blood. Cytase is only active at or near the body-temperature, and is destroyed at 55° C. Amboceptor can act at 0° C., and is not destroyed by heating to a temperature of 55° C.

THE CORPUSCLES.

After a number of paroxysms have occurred in quick succession, the condition of the patient is one of anæmia, and various enumerations have been carried out with a view to finding the nature and extent of changes in the blood-corpuscles. In the case of W. E., I found that the number of red corpuscles per cubic millimetre was, on the morning of March 20, 4,000,000. At 1.30 p.m. he was sent out for a cold walk, and another blood-count was made at 4 p.m. The number was then 3,400,000. At 4.30 p.m. he passed ten ounces of urine containing methæmoglobin. He passed more darkly-stained urine at 6 p.m. and again at 8 p.m. At 10.30 p.m. he passed clear urine, and at 11 p.m. another blood-count was performed. It was then found that the number of red cells was 3,200,000 per c.mm. The next morning, at 10.30 a.m., they amounted to 3,600,000 per c.mm. Three days later, it was found that they had increased to 3,900,000, and on September 20, when six months had passed without a paroxysm, the number was 4,500,000.

The hæmoglobin percentage as estimated by Gower's instrument did not quite keep step with these changes. On the same day, at 11 a.m., the hæmoglobin was 80 per cent.; at 4 p.m., 75 per cent.; at 11 p.m., 65 per cent.; and on the next morning, 70 per cent. Kobler and Obermeyer in their enumerations obtained the following figures:—

		Red corpuscles per cubic millimetre.		Hæmoglobin by Fleischl's instrument.
Before attack	...	3,589,000	...	90 per cent.
During attack	..	2,890,000	...	85 „
After attack	...	3,810,000	...	80 „

These results also show that the young red cells are relatively deficient in hæmoglobin. Mannaberg in his case discovered

most profound anæmia.   His figures were :—

		Red corpuscles.		Hæmoglobin.
In attack ...	...	895,000	...	45 per cent.
1st day after	...	1,500,000	...	45 „
2nd day after	...	3,500,000		
A fortnight later	...	4,390,000	...	60 „

Bristowe and Copeman carried out a series of enumerations on a case in St. Thomas's Hospital and found the same rapid fall in the number of red cells during an attack, with an equally rapid rise when the attack was over, showing that in these cases there is a remarkably rapid reconstitution of corpuscles, although the young corpuscles are very deficient in hæmoglobin.

In cases of paroxysmal hæmoglobinuria in children these variations are even more extreme, and the return to the normal is more strikingly rapid than it is in adults.   The effect of a prolonged stay in hospital, with an equable temperature and favourable surroundings, has a very beneficial effect upon these patients.   Burckhardt reports the case of a boy six years old, who was for six months in hospital, during which time the number of erythrocytes per cubic millimetre increased from 1,500,000 to 6,000,000, while at the same time the hæmoglobin percentage rose from 26 per cent. to 70 per cent.

Examination of blood films, fixed and stained, brings further evidence of the profound disturbance of the erythrocytes.   Films of the blood of W. E., obtained before a paroxysm, show that the red cells are uniform in size and shape, and that the hæmoglobin is equally distributed between them.   After a paroxysm, it is found that they present all manner of sizes and shapes, microcytes and megalocytes (a few), crenated cells, lenticular cells, dumb-bell shapes and the like.   As regards their hæmoglobin content, all stages are found between the deeply-charged cells heavily laden with hæmoglobin and the "ghosts" (Ponfick's "Schatten"), which have lost all their pigment.   Globules of hæmoglobin are seen free in the serum, some of them attached to ghosts, others floating free.   On two occasions I was able in stained films to see basophil punctuation in the red cells similar to that observed in pernicious anæmia and some other conditions,

such as lead-poisoning. In one film, obtained on the day after a paroxysm, there were three nucleated red corpuscles. In wet preparations, it is observed that the red cells have little or no tendency to form rouleaux.

In the preparation of films from the blood of W. E. during, or shortly after, a paroxysm, I found a peculiar difficulty in fixing the film to the slide. The ordinary heat-fixation was quite unsatisfactory; osmic acid was little better, and the alcohol and ether method was the most successful of the means I tried. Stephens and Christopher, in their observations upon black-water fever, found a similar "loss of stickiness."

I did not make any observations upon the specific gravity of the blood, but it would appear from the observations of Copeman that this varies directly with the number of red cells.

My enumeration of the white cells of W. E. gave the following results :—

	Leuco-cytes.	Neutro-phil. per cent.	Acido-phil. per cent.	Small lymphocytes. per cent.	Large lymphocytes. per cent.
Commencement of a paroxysm	9,500	54	2	20	24
After a paroxysm	11,000	68	1	20	11
Three days after a paroxysm	10,000	62	2	22	14
Six months after a paroxysm	9,500	55	1	25	19

This table shows that, during a paroxysm, there is a marked increase in the neutrophil cells, and a less marked in the small lymphocytes. The large lymphocytes, on the other hand, undergo a marked decrease, and, after a paroxysm, the conditions return slowly to the normal. The percentage of large lymphocytes was always above the normal, a condition similar to that which is met with in cases of recent malarial infection.

Mattirolo and Tedeschi publish a case in which there was a leucocytosis before the paroxysm, and a diminution in the number after a paroxysm. In Eason's case, it was found that there was a reduction after a paroxysm.

Donath in 1904 published a case in which the paroxysm was followed by a diminution in the number of leucocytes, thus agreeing with Mattirolo and Tedeschi.

Silbermann was of opinion that there was, in paroxysmal hæmoglobinuria, a destruction or destructive change in the white cells, and that this change was the chief cause of the symptoms attending the paroxysm.

Ruziczka, in his observations upon immunity, has observed that, in the presence of the intermediary-body, the phagocytes are stimulated to great activity in attacking the erythrocytes. He found that, after immunizing guinea-pigs to fowl's blood, the phagocytes were able to destroy the red cells without previously absorbing them, but simply by fixing themselves to one point and nibbling away the cell-substance. Levaditi, Savtchenko, and Grüber also found that erythrocytes loaded with inter-mediary-body are very readily absorbed by the white cells.

Eason, in one of his cases of paroxysmal hæmoglobinuria, found the same exaltation of the phagocytic function and, by analogy with the results of the above observers, attributed it to the presence of intermediary-body.

Bordet was of opinion that the cytases or complements which, in the defence of the body against foreign cells, attacked these cells when they were rendered vulnerable by the amboceptor group, were the products of leucocytes. It has been seen above that, in paroxysmal hæmoglobinuria, a similar toxin is present, and the parallelism between the experiments performed *in vitro* and these observations upon phagocytosis in the presence of intermediary-body is obvious. The explanation must be, that a leucocyte loaded with cytase is attacked by an erythrocyte loaded with amboceptor, and the hæmolytic cycle is complete. In the interparoxysmal periods leucocyte and cytase, amboceptor and erythrocyte are circulating in the blood, and it is not until conditions arise which cause the linking of the amboceptor to corpuscle that the cytase can come into action.

Eason examined microscopically a preparation which showed the action of the hæmolytic serum upon normal blood. In this slide, after the preparation had been left for an hour in a moist

chamber, he observed (1) no formation of rouleaux, (2) variation in the size of cells, (3) poikilocytosis, some of the cells becoming lenticular, (4) a pinkish change in the pigment, (5) no crenation. In a normal control left in the same moist chamber he found (1) general formation of rouleaux, (2) no variation in size of cells, (3) no poikilocytosis, (4) no change in the pigment, (5) distinct crenation. Globules of hæmoglobin may in some cases be seen free in the serum, or irregularly distributed in the cells. Therefore it appears that the leucocytes take an active part in attacking the red corpuscles, and the essential factor in the hæmolysis may be a change in the relations between the red and the white corpuscles.

A pink staining of the plasma precedes the discoloration of the urine. Blood drawn from a finger very shortly after the commencement of exposure to cold shows this; and, on the other hand, at the end of the paroxysm, while the urine is still dark coloured, the blood serum has returned to its normal condition.

In a paroxysm excited by some severe local exposure, such as immersion of the feet in cold water, it is found that the blood at or near the site of exposure undergoes hæmolysis before the blood in some distant part. In blood obtained from a skin puncture in the neighbourhood of the ankle, the serum was quite pink, while a similar specimen obtained from the arm yielded a normally coloured serum. It was further found that, even in paroxysms provoked by a general exposure, the process commenced in the extremities, and a pink serum could be obtained from fingers, toes, and ears at a time when that obtained from some more central position was still normal. This observation makes clear two facts: first, that the circulation in these patients is remarkably slow, and secondly, that hæmolysis undoubtedly takes place in the vessels themselves and not in any of the viscera. Hunter points out this important difference between the pathology of pernicious anæmia and paroxysmal hæmoglobinuria, namely, that in the latter disease the blood-destruction takes place in the vessels and in the former it takes place in the liver.

Before a paroxysm, the serum does not differ in colour from that of a normal person. On the day following a paroxysm, the yellow tint of the serum is deeper than the normal tint. This is probably due to an excess of lutein, the normal pigment of the serum. On a spectroscopic investigation, no absorption bands are revealed. This excess of lutein has also been observed by Stephens in cases of black-water fever. Its significance is not known.

The blood of W. E. was twice submitted to bacteriological investigation. Blood was drawn from a vein in the arm and attempts made to cultivate from it. In both cases a negative result was obtained. Cattle and sheep suffer from an endemic hæmoglobinuria, and in this disease a specific hæmatococcus has been isolated. On the other hand, no organism has been found present in the hæmoglobinuria of horses.

To sum up the blood changes in paroxysmal hæmoglobinuria, it is found :—

1. That in a paroxysm, there is a profound destruction of red cells, followed by an equally rapid re-formation when the paroxysm is over. Evidences of this destruction are obtained, not merely from enumerations, but also from the modifications of the surviving red corpuscles, *e.g.*, poikilocytosis, hypochromasia, and so on.

2. Although reconstitution of blood after a paroxysm is rapid, yet a quick succession of paroxysms strains these powers of reconstitution, and will produce a profound anæmia.

3. There is a slight increase in the number of leucocytes during a paroxysm, especially of the neutrophil corpuscles. The leucocytes appear to participate actively in the process of destruction of red corpuscles.

4. The serum before a paroxysm is normal, and after a paroxysm contains excess of lutein. Soon after exposure to cold, the serum in the extremities becomes pink, and this is followed by a general hæmolysis. The serum returns to its normal colour before the urine is free from its paroxysmal pigments.

THE URINE.

During the intervals between paroxysms the urine passed by W. E. was normal in every respect. Sixty to eighty ounces were passed in twenty-four hours; the reaction was usually faintly acid and the average specific gravity was 1·016. The colour varied from a pale straw colour to a deep amber, and there was little or no sediment. No albumin was present.

The most obvious change during a paroxysm was the change of colour from amber to dark brown or occasionally to dark red. The colour is very intense, and the patient himself called it black. A spectroscopic examination of the urine showed the four absorption bands characteristic of the spectrum of methæmoglobin or of acid hæmatin. These two substances possess similar spectra, and the only test by which they can be distinguished from one another is given by the addition of a reducing substance such as ammonium sulphide. Methæmoglobin then is replaced by reduced hæmoglobin, and acid hæmatin by reduced alkaline hæmatin, and these bodies have different spectra. By means of this test, it was found that the colour was due to methæmoglobin. On one occasion only was acid hæmatin present.

This brown colour was present when the urine was acid. In neutral urine the colour was red, and this was due to the presence of oxyhæmoglobin. Further, if the patient was made to micturate frequently, the urine thus passed was found to be red and to contain oxyhæmoglobin. Therefore it is probable that the pigment passes from the kidneys into the bladder in that form.

It is known that oxyhæmoglobin in the presence of an acid becomes changed into methæmoglobin, and, if the process be allowed to continue further, into acid hæmatin. So that it is highly probable that the colour of the urine depends upon its reaction and upon the time that it remains in the bladder, a long stay in the presence of a highly acid urine changing oxyhæmoglobin to methæmoglobin or even into acid hæmatin.

Dr. Robert Druitt, who was himself a sufferer from this disease and has left behind him an exceedingly graphic account of his experiences, mentions that his urine was at times chocolate

coloured, at times normal in colour, but with a heavy chocolate-coloured sediment, and at times arterial-red in colour, alkaline and intensely irritating.   Murri describes a case in which the urine during a paroxysm was neutral in reaction.   The colour of the first specimen passed was that of malaga.   A later specimen was chianti-coloured.

I next precipitated the blood pigments from the urine and, after filtration, examined it spectroscopically, expecting to find a large quantity of urinary pigments, indicative of increased activity on the part of the liver, but found much less than the normal quantity.   Eason found a similar deficiency of the urinary pigments, and concluded that, in a paroxysm, the liver, far from being overtaxed, was doing less than its usual work.

During a paroxysm there was a slight decrease in the amount of urea excreted.   This agrees with the observations of Prior, Fleischer, and others.   Gillespie, on the other hand, found an increase in the quantity of urea.   It is also stated by most authorities that the total nitrogen in the urine is diminished. Eason, moreover, found that the percentage of urea nitrogen, which during the intervals was 88·5, the normal figure, rose during a paroxysm to 99·6 per cent. and fell again on the day after the paroxysm to 86·4 per cent.

The phosphoric acid is diminished, and Murri and others have found that, in spite of the extensive cell-destruction, there is no increase in the quantity of chlorides.

From these observations it appears that there is a slight diminution in the excretion of waste products.   But cold and over-exertion, the agents in the production of a paroxysm, would both increase the waste products in a normal individual : cold by causing increased metabolism in order to maintain animal heat, and exertion by the result of muscular activity.   So that there is apparently a retention of waste products during a paroxysm.

There is no change in the quantity of urine passed, but in most of the paroxysms there was a tendency to frequent micturition. The urine was slightly more irritating than at other times.   This was especially noticeable on the occasions when the urine was alkaline and consequently of a bright red colour.

In the intervals between the paroxysms, there was little or no sediment, but the paroxysmal urine contained a heavy sediment, usually of a brownish colour. A microscopic examination of this sediment reveals the presence of a very few red corpuscles—perhaps one in two fields—an occasional ghost, and some pigment granules. There are also to be found granular hyaline and a few pigment casts, as well as a number of calcium oxalate crystals. In the urine of W. E. no epithelial casts were found, but Murri found them in one of his cases.

Albumin appears in the urine at a very early stage in the paroxysm, before the colour is changed. It also persists after all the hæmoglobin has been discharged, even for two or three days after a paroxysm. In the case of a child, who was in the hospital in January of this year, it was found that albuminuria persisted for four or five days after a paroxysm. In no case on record is there a history of persistent albuminuria.

Sometimes, in the words of Strumpell, " Bei leichten Anfällen kann es nur zu Albuminurie ohne Hämoglobinurie kommen." A mild exposure to cold will cause a moderate degree of hæmolysis : the liver will effect the elimination of the hæmatin moiety and the globulin will pass out through the kidneys. Globulinuria is, in these cases, a more precise term than albuminuria, as the proteid in the urine is pure globulin. Bristowe has felicitously described these abortive paroxysms as the *petit mal* of hæmoglobinuria.

But paroxysmal globulinuria occurs in many cases which have never suffered from the corresponding *grand mal.* The inter-mittent albuminuria that follows bathing and such exposure was described by Dr. George Johnson in 1873. Under the name of periodic or cyclic albuminuria, it is recognised as an exceedingly common condition in young adults. It occurs less frequently in schoolboys. Exercise, fatigue, and exposure to cold are the most commonly recognised causes. Although essentially an ailment of youth which may disappear with advancing age, it is now recognized that many persons so affected in their youth become later the subjects of chronic nephritis. No case is recorded in which periodic albuminuria of adolescence has gone on to

paroxysmal hæmoglobinuria in later life, and it is probable that the resemblance between the conditions is superficial, and does not imply any kinship between the essential pathological causes which underlie them.

EFFECTS OF COLD: CUTANEOUS MANIFESTATIONS: TEMPERATURE.

Patients with paroxysmal hæmoglobinuria are remarkably sensitive to external cold, and in the severer cases there is " extreme difficulty in maintaining animal heat." These are the words of a patient. The circulation is usually extremely sluggish, and there is a tendency to " dying of the fingers " and similar discomforts. W. E. was a person of sallow complexion, but on exposure to cold his face became cyanotic, his lips blue ; his skin generally became mottled and his fingers dead. Exercise had no warming influence ; in fact, he said that work made him feel colder. Dr. Druitt has given a graphic description of his own sensations. The illness began at Cambridge in 1867, when the patient " believed himself to have been poisoned whilst hanging over the once beautiful streams at the backs of the colleges, then polluted with sewage." After a moment's exposure to a cold wind, the face would become blue and the point of the nose almost black. This was so marked that it attracted the attention of passers-by. His ears were subject to frost-bite, his fingers were continually dead, and he suffered from chilblains.

In W. E. I found that the capillary reflux on the back of the hand was three times as slow as in a normal person. At one observation the time of reflux in my hand was four seconds, and in the patient's hand twelve seconds. The reflux in the case of the child was complete in ten seconds, as compared with five seconds in a normal person.

But these are not the only cutaneous manifestations met with. Purpura, urticaria, and circumscribed œdema have been described. In a case described by Wilks, the patient was cyanosed, the hand was at first blue and painful, and later there was dry gangrene of the fingers.

It has been already remarked that the sequence of events within the blood-vessels cannot be deduced from the behaviour of

blood *in vitro*. Donath states that the processes are at least analogous : " Durch Abkühlung und folgende Erwärmung des Hämoglobinurikerblutes *in vitro* erhält man ein Paradigma des durch Kälteeinwirkung verursachten Anfalles." But apart from the fact that the corpuscles so treated become, from the very methods of the experiment, unstable, it is obvious that the circulating blood is in no case directly exposed to this extreme of temperature. In one of Copeman's cases, it was found that exposure to a temperature of 51° F. would cause a paroxysm— a temperature that was usually without effect upon the blood contained in a test-tube.

The influences of external cold may reach the blood within the vessels in two ways. It may directly chill the blood at or near the surface—say, within a range of two millimetres from the surface—or it may act indirectly, through the nervous system, sending impulses along a path analogous to, if not identical with, the vaso-motor arc.

If this latter hypothesis be accepted, it follows that a contributory cause of the paroxysms may be found in the nervous system. Murri was of opinion that there was in these cases an abnormal excitability in the vaso-motor nerve centre, and claimed support for this hypothesis from the associated evidences of vaso-constrictor spasms, urticaria, cyanosis, and so on. Further, in cases of paroxysmal hæmoglobinuria due to causes other than cold, there is a similar reflex ; inanition hæmcglobinuria is caused by a reflex which starts from the walls of the stomach, and menstrual hæmoglobinuria by one from the walls of the uterus, while after severe exertion a " hæmoglobinuric reflex " starts from the muscles and travels along the muscle sense fibres.

Murri considered that hæmoglobinuria in these cases was due primarily to a slowing of the circulation in the distal parts of the circulation. Chvostek administered amyl nitrite to one of his patients, and found that, if administered at the beginning of a paroxysm, it would mitigate or even inhibit the paroxysm. " Es gelingt den Paroxysms so zu beeinflussen, dass, wenn die Anwendung frühzeitig erfolgt, es bei den Prodromalsymptomen bleibt, und dass die Application, selbst in ausgesprochenem Paroxysmus,

denselben zu coupiren vermag, und bewirkt, dass er ein abortiver wird."

Chvostek performed an interesting series of experiments upon horses, in which he found that by stimulating the spinal cord in the cervical region he could produce hæmoglobinuria.

The boundary between paroxysmal hæmoglobinuria and Raynaud's disease is very vaguely defined, and the above remarks may seem perhaps more appropriate to the latter ailment. The symptom-complex that is characteristic of Raynaud's disease differs in degree only from that of paroxysmal hæmoglobinuria. If the vaso-constrictor spasms form the most prominent part of the clinical picture, the diagnosis of Raynaud's disease is made ; if these symptoms are subsidiary to the intermittent hæmolysis, the alternative title is employed. Both conditions are rare, and it is impossible to regard their so frequent co-existence as fortuitous. From collected statistics it appears that 6 per cent. of patients with Raynaud's disease pass hæmoglobin in the urine ; and, on the other hand, a large number of patients with paroxysmal hæmoglobinuria suffer from localized asphyxias, more or less severe. The cutaneous vaso-motor reflex causes, in the one case, an abnormal constriction of the vessel-walls, and in the other case an actual disintegration of the formed elements of the vessel-contents. It has been thought by some authors that the hæmolytic toxin is secreted by the vessel-wall, but there is no direct evidence for this view. On the other hand, if the excretion of waste products does not increase *pari passu* with the over-production due to cold or exertion, or whatever has caused the paroxysm, it is logical to surmise that the waste products so retained, and brought into intimate relation with the formed elements of the blood, or with the vessel-wall, might with the co-operation of an unknown factor cause the disintegration of the former and consequent hæmoglobinæmia, or the spasmodic constriction of the latter with resulting local asphyxia. And in the case of the disease now being discussed, this unknown factor is in all likelihood the potential toxin whose existence has been proved in some previously described experiments.

The degree of cold which suffices to fire this train, so to speak, varies in different cases. One of my patients, the most intelligent of the three, informed me that in his case a paroxysm always followed exposure to a temperature of 40° F. In one of Copeman's cases it is recorded that a bath of ten minutes' duration in water at 51° F. would produce au attack. The most common history given is that the initial paroxysm followed an exceptionally severe chill, and that subsequent paroxysms were the result of a much more trifling stimulus. W. E. passed hæmoglobin in his urine for the first time after a very cold day's work in dry dock. Another patient recently in Guy's Hospital passed hæmoglobin in the urine after an attempted suicide from London Bridge and a consequent severe chilling. A certain physician, now deceased, was seized with his first paroxysm of hæmoglobinuria after a cold and wet day's fishing in Scotland. His second attack was also the result of a wetting in the Highlands, but thereafter these attacks would be evoked by some much more trivial cause—a moment spent in the open air without an overcoat, even the very trifling exposure involved in opening a window, would determine an attack. Concurrently with this increased irritability or instability of the blood corpuscles there is an aggravation of the subjective symptoms caused by cold; in fact, the two phenomena would appear to bear a constant proportion to one another, so that a patient is usually able to know from his own sensations whether an attack be imminent or not. It has been seen, from the account of Dr. Druitt's case, that the subjective phenomena form no small part of the sufferings of these patients.

The mouth-temperature of W. E. during the interval was usually between 97° and 98° F., and did not vary beyond those limits except during a paroxysm. At the commencement of an attack there was a depression of temperature to 96° or 96·4°, and this was followed by a rapid rise of temperature to 101° or 102°. The maximum temperature usually coincided with the first appearance of pigment in the urine. After this the temperature fell gradually during the next two or three hours to 98°. After one paroxysm, the most severe that he experienced while in the

hospital, the temperature fell to 96°, and there was then a slight
secondary rise to 99°.   In the case of my other patient, the
temperature did not rise above 100°.   In about half of the cases
described, there is a marked rise of temperature, synchronous as
a rule with the height of a paroxysm, and this instability of
temperature is specially marked when the disease occurs in
children.   In extreme cases, the temperature will, after a
preliminary fall to 95°, rise in three hours to 104°.   On the
other hand, in many cases, extensive hæmolysis occurs, and yet
the rise of temperature is trivial.

Although it must not be overlooked that the records of cases
in which the rise of temperature is most marked come principally
from the earlier literature, and it is possible that there may have
been a confusion of diagnosis, yet even in the most recent
cases a temperature of 101° or 102° is the rule rather than the
exception.   It is probable that the rise in temperature is due
both to increased heat production from increased metabolism,
and to diminished heat loss due to the ischæmic condition
of the skin.   In this connection, however, I must mention
some rather paradoxical observations of Murri on the surface
temperature during an attack.

He found that if his patient Bertozzi and a healthy person
were exposed to the same atmospheric conditions, there was
considerable divergence between the ratio of skin temperature
to body temperature in the two cases.   These differences were
specially marked if they were exposed to a degree of cold
sufficient to induce in Bertozzi a paroxysm.   Both patient and
healthy subject had their feet immersed in cold water for a
quarter of an hour, and then the foot-bath was withdrawn.   It
was found that the surface temperature in the extremities, hands,
feet, and so on, fell more in the case of Bertozzi than in the
normal person.   In some other positions, however, the surface
temperature was higher in Bertozzi than in the other, and during
the two hours following the experiment the temperature in these
positions rose higher and higher.   These positions were the
back of the thigh and the small of the back.   Murri's explanation
of these phenomena is, that there is in hæmoglobinurics a greatly

increased heat production, and that the skin in the areas which lie over the great muscle-masses—the principal sites of heat-production—becomes consequently warmer than the corresponding areas of skin in a normal person under like conditions.

MORBID ANATOMY.

Paroxysmal hæmoglobinuria is not dangerous to life. There is no record of any uncomplicated cases which have proved fatal. Occasionally, however, general tuberculosis or aortic disease may supervene, and I have been able to find accounts of four post-mortem examinations. Murri's patient, Isaia Giovannini, died in 1877 of general tuberculosis. Tubercles were found widely distributed. The kidneys were hyperæmic, there was an excess of interstitial tissue unevenly distributed, and the cortex was hypertrophied. The epithelium of the convoluted tubules showed signs of degeneration. There was a peculiar congenital displacement and malformation of the right kidney. The lymphatic glands round the aorta and the vena cava were much enlarged.

Three days after the above autopsy took place, Demarchi Clemente died at Pavia. He had suffered from " emoglobinuria dal freddo " for five years. The autopsy was performed by Stefanini, with the assistance of Golgi. The arteries were atheromatous. The liver was quite normal, but the spleen was nearly twice the normal size. The kidneys were enlarged ; the capsule stripped readily. The cortex was easily lacerated and the surface was marked with dark rose points. The medullary pyramids were hyperæmic and showed distinctly many red striæ. Microscopically he found " una leggere nefrite diffusa e special- mente interstiziale." The patient died from aortic disease, and it is probable that these were " cardiac kidneys."

Prior reports an autopsy in which nothing remarkable was found. Widal describes a deposit of pigment in the kidneys similar to that found in cases of malarial cachexia by Kelsch and Kiener.

The organs that demand most attention are naturally the kidneys. It was thought first that blood-pigment appeared in

the urine as a result of morbid changes in the kidney—that the disease was local.   When the presence of free hæmoglobin in the circulating blood was discovered, the problem became much more difficult.   In a paroxysm, albumin and hæmoglobin are found in the urine.   Granted that they are derived from the destruction of erythrocytes, how do they contrive to traverse the renal filter? The molecule of hæmoglobin may pass more easily than that of globulin through the filter, yet even then it is difficult to understand how it traverses the healthy kidney.   It is true that in the two autopsies reported by Murri there was, in point of fact, some degree of nephritis.   But, on the other hand, there is in the majority of reported cases strong evidence that the kidneys are healthy.   In all three of my cases, the interparoxysmal urine was perfectly normal.   In W. E. the paroxysmal sediment was frequently submitted to minute and careful examination and no epithelial casts were found.   Epithelial casts are occasionally met with, and it is notable that they were found by Murri in the case of Giovannini.   Perhaps in the small number of cases in which these have been found there was some degree of nephritis. On the other hand, Litten, in a study of hæmoglobinuria in animals, found that there was no nephritis, even though albumin persisted in the interparoxysmal urine.

In the case of Giovannini reported above, Murri was of opinion that there was an active hyperæmia in the glomeruli to which the ischæmia of the skin and obstruction from the large abdominal lymphatic glands contributed.   Whether the pigment passes out in the glomeruli or by the convoluted tubules, there are two views.   Forsbach was of opinion that the hæmoglobin passed out by the glomerular route, and that the tubules did not participate in its elimination.   Christomanos, on the other hand, found hæmoglobin droplets in the tubular epithelium, while at the same time Bowman's capsule was quite free from hæmoglobin. It is certain that the tubules frequently have their lumen entirely occupied with hæmoglobin, as hæmoglobin casts appear in the urine.   Stempel states that, in paroxysmal hæmoglobinuria, the pigment may block the tubules so as to cause uræmia, but I have been unable to find any record of such an event.

In the introduction to this paper, it was pointed out that
hæmoglobinæmia was followed by hæmoglobinuria only when
the liver was no longer able to cope with the abnormal conditions.
A lesser degree of hæmoglobinæmia was followed merely by
greater activity on the part of the liver, an increased secretion
of bile, and an increase in the urinary pigments. The scanty
evidence afforded by post-mortem records shows that there is no
organic change in the liver, but from clinical observation it is
obvious that the liver does participate in the paroxysm. In
the case of W. E., the liver during an interparoxysmal period
was palpable about a quarter of an inch below the costal margin.
At the onset of a paroxysm it increased considerably in size and
reached to a line an inch and a half or two inches below the
costal margin. When thus enlarged it was slightly tender. This
enlargement of the liver is mentioned in all the most detailed
descriptions of cases, and in only one case is it specifically stated
that the liver was not enlarged. It is therefore justifiable to
assume that a paroxysm is accompanied by an enlargement of
the liver in a typical case of the disease. But from the above
" overflow " theory of hæmoglobinuria, it follows that a paroxysm
should be accompanied by the clinical manifestations of an excess
of bile ; and it is certainly true that such alimentary disturbances
as diarrhœa and bilious vomiting do not infrequently accompany
a paroxysm. Jaundice is less common, and would not occur
unless some slight local obstruction was present. In none of my
cases was jaundice present. One of them presented a lemon
tint similar to that characteristic of pernicious anæmia. Occa-
sionally during a paroxysm there was a peculiar yellowish
discoloration of the sclerotic, due probably to free hæmoglobin
having penetrated into the lymph channels. In view of this
apparent increase in the activity of the liver, it is surprising to
find that very little urobilin is present in the urine. After
hæmoglobin has been removed by precipitation, the urine is
found to contain only the merest trace of urinary pigment, and
this has led competent observers to the opinion that the liver is
not abnormally active during a paroxysm, that, on the contrary,
there is an inhibition of its normal functions, and that this

inhibition is a contributory cause of an attack. Against this view must be placed the fact that the fæces contain as large a quantity of bile as at ordinary times, and that alimentary disturbances due to hypercholia are of frequent occurrence.

In a large number of the cases reported it is stated that the spleen becomes large and hard during a paroxysm. This is a more obvious change than the enlargement of the liver, and is mentioned in several accounts in which there is no reference to the liver. In the case of W. E., the spleen became doubled in size and easily palpable. The outline of the spleen could easily be seen if the abdomen was carefully watched during deep breathing. The organ was at the same time rather tender. In one of the reported autopsies the spleen is described as large and hard, but no microscopic examination was made. It cannot be stated precisely what the significance of this enlargement of the spleen really is, but it may fairly be surmised that the products of blood destruction accumulate in that organ. Stempel is of opinion that the cell-wrecks (Zelltrümmer) are retained by the spleen, which swells in consequence. Reference has been made to the presence of ghosts in the blood during a paroxysm, but their fate has not been made clear. Such débris forms only a trifling portion of the urinary sediment. Litten, in his researches on some animals that had long suffered from hæmoglobinuria, found in the spleen large cells rich in protoplasm and laden with hæmoglobin droplets and damaged erythrocytes. He also found a hyperplasia of the red marrow. Analysis of the urine, as has been seen, shows that, in spite of the extensive cell-destruction that occurs during a paroxysm of hæmoglobinuria, there is no increase in the elimination of chlorides, or of the total nitrogen. It has also been seen that the number of erythrocytes returns to the normal in a very short time after the end of an attack. All these facts combined would appear to point to a plausible hypothesis, namely, that the broken-down cells, ghosts, and other débris—the killed and wounded left on the field after a paroxysm—are not completely destroyed and eliminated, but are collected in the spleen ready to be worked up again at the right time and place into new erythrocytes.

SYPHILIS AND PAROXYSMAL HÆMOGLOBINURIA.

The effect of syphilis upon the blood has received more attention from observers abroad than from those at home. The first research upon the subject was that of Wilbuscevick, in 1874, who found in cases of syphilis that the red corpuscles were diminished and the white corpuscles increased. Upon the administration of mercury the red corpuscles became at first more numerous and the white cells fewer, but when a certain point in the treatment was reached the red cells again diminished. These opinions were confirmed by other observers. Bieganski found that in primary syphilis the number of red cells was not diminished, but their hæmoglobin content was much reduced. The white cells became more numerous, the increase in the number of lymphocytes being particularly marked. After a course of treatment with mercury, the red corpuscles were increased and the hæmoglobin percentage became normal. The number of white cells was diminished. Konried came to the conclusion that the hæmoglobin moiety of the red corpuscle could resist the syphilitic virus less than the stroma. In untreated cases he observed that, with spontaneous involution of the symptoms of syphilis, the condition of the blood returned to the normal. On the other hand, if the symptoms became aggravated, the quantity of hæmoglobin became markedly reduced and severe syphilitic anæmia ensued.

Important work on this subject has been carried out by Murri and Justus. Their later researches throw a sidelight upon the relation between syphilis and paroxysmal hæmoglobinuria, and so point to a solution of the most important problem in the etiology of the disease.

Justus, by means of injection or inunction, administered mercury to a number of syphilitic patients, and observed the consequent variations in the percentage of hæmoglobin. He found that, in an ordinary case of syphilis, the initial injection of $\frac{1}{2}$ milligramme of corrosive sublimate was followed by a 10 or 20 per cent. fall of hæmoglobin. A second injection three or four days later was followed by a slighter fall, and after this a continuation of the treatment would slowly bring the hæmoglobin

percentage back to the normal figure. In cases of severe syphilis, or in cases where syphilis was complicated by an intercurrent disease, these falls in hæmoglobin percentage after mercurial injections persisted for a longer period. If, in a severe case of syphilis, the blood is examined shortly after an injection of mercury, it is found that the destruction of corpuscles has been extensive enough to give the serum a pink tint. This reaction was considered by Justus to constitute an important test in doubtful cases of syphilis, but there has been considerable difference of opinion as to its usefulness.

Murri obtained blood by venesection from thirty syphilitic patients and divided each specimen into two portions. One series was allowed to clot at 20° C., while the other series was exposed to a temperature of 2–3° C. In the former series, the serum that separated out was normal in colour, but of those that had been exposed to cold, the serum in twenty-eight cases was pink. In some syphilitic patients, Justus was able to produce hæmolysis by brief elastic constriction of the arm. In others he repeated the classical finger experiment associated with the name of Ehrlich. He placed an elastic band round the base of a finger and found that the stasis caused by this band had sufficed to produce hæmolysis. No application of cold was necessary. Ehrlich made his patient put the finger, thus isolated, in ice-cold water for a quarter of an hour, and then allowed a specimen of blood obtained from the finger to clot. He found that extensive hæmolysis had taken place. The experiment has been repeated by Boas, Copeman, and many others. Chvostek found, like Justus, that stasis without cooling was in some cases followed by hæmolysis.

There is no doubt that the majority of patients with hæmoglobinuria have had syphilis. A number give a history of syphilis; in others a systematic examination reveals traces of infection. It is noteworthy that some of the cases—a relatively large number—give a history of very severe secondary symptoms; and in a number of cases of paroxysmal hæmoglobinuria, there exists also some definitely post-syphilitic lesion. In one case the patient suffered also from aneurysm; syphilitic arteritis is a

frequent complication, and aortic disease of specific origin has also been found in this series. W. E. was a notable example of how a number of these paraluetic conditions may co-exist. In February of last year, on admission to the ward, it was found that he had aortic disease. His nervous system was also examined and nothing abnormal was found. In September, on readmission, locomotor ataxy was discovered in addition to his other troubles. He had in six months developed all the classical signs of this condition. The knee-jerks had disappeared, testicular sensation was absent, Romberg's sign was present, he had Argyll-Robertson pupils and abnormalities of gait were just becoming perceptible.

When paroxysmal hæmoglobinuria occurs in children, there is usually an hereditary taint, and concomitant signs such as keratitis punctata, quiet effusion into joints, rhagades, and the like are described.

From the records of Guy's Hospital, and from the literature, I have collected thirty-nine cases of paroxysmal hæmoglobinuria; thirty of the patients were men. The age distribution was as follows: under 10 years there were nine cases; between 10 and 20, five cases; between 20 and 30, seven cases; between 30 and 40, eight cases; between 40 and 50, eight cases, and between 50 and 60 there were two cases. Acquired syphilis was an antecedent in seventeen cases; seven cases showed evidences of congenital syphilis; seven cases were doubtful, and in eight cases it is definitely stated that there was no history or evidence of a specific infection. The interval between the primary invasion of syphilis and the initial paroxysm of hæmoglobinuria was in one case as short as eighteen months, in another case as long as twenty years. The average interval is seven years.

Stempel collected seventy-seven authenticated cases of paroxysmal hæmoglobinuria and found a syphilitic history in only 29 per cent. of them. The statistics quoted above show 60 per cent. It cannot be affirmed, therefore, that every case has a syphilitic origin, although in the majority of the cases the first cause of paroxysmal hæmoglobinuria is without doubt syphilis.

What, then, is the connection between these two diseases? The researches quoted at the beginning of this section show that the virus of syphilis has a profoundly deleterious influence upon the blood and causes a distinct lessening of the stability of the erythrocytes. There are a number of ways in which this may have been brought about, and consequently there is prevalent a large number of conjectures. Most of these views it is at present quite impossible to prove or disprove. The oldest hypothesis is that syphilis so affects the blood-forming organs, that they produce red corpuscles of greatly diminished powers of resistance to hostile influences. Others, using a different expression, say that the effect of syphilis is to modify the stroma of the red corpuscles, so that it is no longer capable of holding firmly the hæmoglobin moiety, that the link between stroma and hæmoglobin is less firm than in the healthy person. Others say that there is a chemico-physical change, a modification of the cholesterin envelope or a diminution in the surface tension of the corpuscle. Chvostek has shown that simple mechanical shaking of the blood *in vitro* may cause hæmolysis. All the hypotheses agree in substance, indicating that the red corpuscles are more than usually vulnerable to attack, and postulating a hostile agency ; but for the most part they are silent as to the nature of this agency. It has been shown in a previous section that there is in the serum of paroxysmal hæmoglobinurics a potential toxin; but that the erythrocytes are abnormally vulnerable is doubtful. I found that the serum of W. E., when added to my own red corpuscles, produced a hæmolysis no less profound than that which followed its action upon the disease corpuscles— that, in other words, the serum was not only autolytic but also isolytic. Perhaps—I had no means of exact measurement—the action upon healthy corpuscles was the more profound as there would not in healthy blood be any tendency to the formation of anti-autolysins. Eason has in his more recent work found that such bodies are actually found in the blood of hæmoglobinuric patients.

It would be instructive to discover whether the serum in syphilitic persons is ever isolytic, whether it would have any

deleterious influence upon healthy corpuscles. As far as I am aware, no research of this kind has been carried out.

THE RELATION OF PAROXYSMAL HÆMOGLOBINURIA TO MALARIA, ETC.

It is usually stated in text-books that, after syphilis, malaria is the most frequent antecedent of paroxysmal hæmoglobinuria, but in my series of forty cases only two were associated with malaria. One of these malarial cases had also had syphilis, and in the other case syphilis could not be definitely excluded. An examination of the literature shows that cases which give a history of malaria were much more common thirty years ago than they are at the present day. Wickham Legg, writing in 1874, stated that one-third of the cases described gave a history of malaria : in 1908 malaria is recorded in 5 per cent. of the cases.

This discrepancy suggests that there was in the early days a confusion between paroxysmal hæmoglobinuria and black-water fever. There is clinically a considerable resemblance between a mild attack of black-water fever and a severe paroxysm of hæmoglobinuria ; and further, there is a number of changes in the blood, liver, and spleen common to the two conditions. If it could be definitely proved that one case of authentic paroxysmal hæmoglobinuria—" hæmoglobinuria a frigore "—owed its origin to a malarial infection, then the affinity between the two conditions would be made closer. But there are no records of such a case.

Stewart's patient in Archangel in 1792 was successfully treated with quinine, but it is extremely doubtful whether this was actually a case of paroxysmal hæmoglobinuria. Quinine was used in many cases more recently recorded, but without much success. Mercury has had better results.

For a short period in September I administered quinine to W. E. in increasing doses, in order to ascertain whether it was possible to precipitate a paroxysm by such treatment, and in this I was unsuccessful. In a few days I had increased the dose so that the patient was taking thirty grains in twenty-four hours. This dose caused deafness and digestive disturbance, but it had

no effect on the urine. I was then obliged to stop the administration, as the discomfort produced was so extreme.

Rheumatic fever, enteric fever, and prolonged suppuration have been adduced in a few cases as possible antecedents of paroxysmal hæmoglobinuria. Heredity, apparently, has played a part in a few cases. The case in which paroxysmal hæmoglobinuria followed prolonged suppuration is suggestive, in view of the fact that prolonged suppuration and syphilis are the two commonest causes of lardaceous disease.

CONCLUSIONS.

1. Paroxysmal hæmoglobinuria is the result of intravascular hæmolysis.

2. This intravascular hæmolysis occurs when the blood serum becomes autolytic. There is in the blood serum a potential toxin, composed of cytase and amboceptor, which becomes active under certain conditions.

3. The most prominent of these conditions is the application of external cold. In experiments *in vitro* it appears that direct application of cold will activate the serum. *In vivo* it is most probable that the application of cold sends impulses to the vessels by the vaso-motor arc—that the hæmolytic reflex travels by the same path as the vaso-motor reflex.

4. Similarly in examples due to the less common causes, inanition, menstruation, or exertion, hæmolytic reflexes start from the stomach, the uterus, or the muscles respectively.

5. Variations in the severity of the paroxysm may depend upon variation in the excitability of the nerve centres. When these are unusually excitable, a paroxysm is more readily produced than when they are quiescent. This perhaps accounts for the fact that while the initial paroxysms in such patients are due to a very severe chilling, the subsequent paroxysms start from a much more trivial cause.

6. Paroxysmal hæmoglobinuria and Raynaud's disease are closely related, and the boundary line between the two conditions is indefinable. The vaso-motor disturbances characteristic of the latter disease are frequent in paroxysmal hæmoglobinuria,

and 6 per cent. of patients who suffer from Raynaud's disease pass hæmoglobin in the urine.

7. A paroxysm is attended with great degeneration and destruction of the red corpuscles. The number of leucocytes is not greatly altered, but they participate actively in the process of hæmolysis. Autolysis or heterolysis is always accompanied by exaltation of the phagocytic function ; that is to say, in the presence of amboceptor the leucocytes are stirred into great activity. It is probable that the leucocytes are the source of the cytases.

8. The serum of paroxysmal hæmoglobinuria is isolytic as well as autolytic : *in vitro* it can destroy the corpuscles of a normal person as well as those of a patient. It is not therefore necessary to assume any specific vulnerability in the red corpuscles in this disease.

9. After a paroxysm the reconstitution of the blood is very rapid, and this, coupled with other observations which need not here be recapitulated, suggests that the products of cell-destruction are largely retained to form the raw material for a new generation of erythrocytes.

10. The ultimate source of the hæmolysin is not known. Syphilis is a possible antecedent in a majority of cases, but the disease is not invariably syphilitic. Other antecedents, far less common, have been mentioned. In syphilitic patients generally, there is frequently a lack of stability in the blood which has a very suggestive resemblance to the conditions present in hæmoglobinuria.

11. There are no gross organic changes in the abdominal viscera. The liver is enlarged during a paroxysm. The spleen also, possibly from an accumulation of waste products, becomes bigger. There is possibly a passive hyperæmia of the kidneys, but no inflammatory change.

12. Granted that, on the one hand, the blood circulating within the vessels contains a potential toxin which on the receipt of appropriate stimuli becomes actively hæmolytic, and that, on the other hand, these stimuli, whatever their origin, reach the vessels by the vaso-motor nerve fibres, it would appear that there is still

a missing link.   The nerve endings are situated in·the vessel-wall
and have no direct communication with the blood itself.   There
is no evidence, histological or experimental, to support the view
that a secretion is poured out by the endothelial cells in response
to secreto-motor stimuli.

Twenty-five years ago an Italian author said that, in his
opinion, paroxysmal hæmoglobinuria was due to "una discrasia
sanguigna essenziale," and since his day there have been many
sesquipedalian confessions of ignorance.   Nowadays, it is
possible to study with exactness paroxysmal hæmoglobinæmia as
it occurs in a test-tube, and it can fairly be claimed that the
existence of a specific toxin has been proved.   But there is still
an unknown quantity, a gap in our knowledge of the sequence of
events.   No line of investigation hitherto suggested promises to
give a solution of this problem.   Until new methods or more
perfected methods make such investigation possible, there will be
no end to vague speculations.

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TEN CASES OF BRAIN ABSCESS.

By

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In the past three years ten cases of brain abscess have come under my care, and as they form a consecutive series, illustrating many interesting points, I have analysed some of their chief features in the following notes :—

CASE 1.—George B., æt. 17, was admitted into Barnabas ward under my care on March 6th, 1906, suffering from chronic left otorrhœa and cerebral symptoms. The left middle ear suppuration began in 1879, when an operation for acute mastoid abscess was performed and polypi were removed. In February, 1906, a swelling appeared behind the left ear with headache and photophobia, which were relieved after a superficial post-auricular abscess had been opened. On March 2nd, after walking seven miles, the patient noticed that he had diplopia; he then lost the use of his legs and became unconscious, and was found lying in the road. The next day he was better, but was sick once, and on March 5th he could not read certain words. He was seen by the late Dr. Cooper, of Southwark Park Road, who, finding that he was sick and could not read, and suspecting an intracranial abscess, sent him up to Ear Out-patients, where he first came under my notice. On admission his temperature was 99°, pulse 100, respiration 20; there was a sinus behind the left ear and pus in the meatus; there were no urgent symptoms, and for the next two days the pulse rate ranged between 72 and 92, and the temperature was 98–99·8°. On March 9th a left radical mastoid operation was carried out, and in doing this the roof of the attic and antrum was found to be considerably eroded, exposing the dura mater over the temporo-sphenoidal lobe; the dura was covered with granulations; the pulsation of the subjacent brain appeared normal. For the next two days the patient's condition was satisfactory, but on the 11th his pulse varied between 60 and 68, and on the 12th between 60 and 72. On the 13th it fell from 68 to 56; his cerebration was now noticed to be very slow, he was drowsy, and early double optic neuritis was detected. There was paresis of the left external rectus muscle producing homonymous diplopia; at 7 p.m. the pulse rate fell to 49, and immediate operation was undertaken for cerebral abscess. When the old incision was opened up, the dura which had been found exposed at the

previous operation was seen to bulge, so more bone over the antral and attic roofs was removed and the bulging dura was punctured in several places with an exploring needle, but no pus was found. As this seemed unsatis- factory, a free incision was made with a scalpel through the centre of the area of granulating dura ; after the knife had penetrated the latter and a thin layer of adherent cortex, a quantity of watery, foul-smelling pus was evacuated ; the finger was then passed into the cavity in order to estimate its size, when the floor formed by dura and cortex was so freely excised as to allow the roof of the abscess cavity to be pushed up to the surface by the cerebral pulsations. About one ounce of pus was evacuated and the cavity was drained with a rubber tube ; no stitches were inserted. Dr. Eyre reported that the pus contained streptococcus longus. The patient's mental condition soon improved and he became much brighter, his pulse varied from 68 to 98. On March 14th right infra-nuclear facial paralysis was found ; the diplopia had not altered since the operation, both external recti being weak. The pulse was normal and the general condition good ; there was marked optic neuritis. On March 22nd it was noted that the patient could not read or write correctly ; though he spoke intelligently and could copy ; he forgot the names of things. Dr. Pitt and Mr. Eason saw him and agreed that the post-operative symptoms were due to serous meningitis. After this he rapidly improved ; on the 26th the facial paralysis was almost gone and the squint was much less ; a few days later both had disappeared. On April 2nd an anæsthetic was given in order to replace and suture over a small cerebral hernia, but this was not very successful, as the wound suppurated and eventually healed by granulation. After discharge on May 9th the patient attended the Out-patient Department for several months, and has been seen at intervals of six and twelve months up to the summer of 1908, when he was absolutely normal except that the left ear, which is quite dry, is very deaf.

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Case 2.—Emma A., æt. 11, was admitted into Martha ward under Mr. Lane on August 31st, 1907, for chronic otorrhœa with pain in and swelling over the left mastoid antrum. The usual crescentic incision behind the left ear opened a subperiosteal abscess, and by following a fistulous track through the bone into the antrum the House Surgeon carried out the operation of antrectomy after Schwartze's method. Over the roof of the cavity the dura mater lining the middle fossa had been exposed, quite unavoidably, and in order to remove some overhanging bone near this I took the operation in hand, when with a large gouge I wounded the dura and penetrated the temporo-sphenoidal lobe for some distance. The whole wound was drained and the patient did well until September 9th, when left external strabismus, with ptosis, was noticed. During the previous week the pulse rate had varied from 68–80, and the temperature between 98·4–100° F. Mr. Eason examined the patient and found definite optic neuritis, with paralysis of the extrinsic ocular muscles supplied by the left third nerve. The above combination of symptoms, with the knowledge that the temporo-sphenoidal lobe over the antrum had been injured made the diagnosis of temporo-sphenoidal abscess easy. The patient was anæsthetised, and the dura mater was freely incised with a scalpel where it had been exposed by the previous operation, when about two ounces of foul-smelling pus were evacuated from the third temporo-sphenoidal convolution. It is interesting to note that before the

dura mater was freely incised an exploring needle was inserted in exactly the same position, and yet no pus was withdrawn. The ocular paralyses were unnoticeable on September 10th, but the optic neuritis remained unaltered until after September 24th; on September 30th Mr. Eason noticed that it was decreasing. Two days later the temperature was 97°, the pulse 72, and respirations 20. The optic neuritis gradually diminished and the external wound healed. The patient left the hospital on October 3rd, 1907, quite well.

CASE 3.—Albert H., æt. 18, was admitted into Barnabas ward under my care on November 6th, 1907, for an acute subperiosteal mastoid abscess on the right side. He had had suppuration in this ear for three years, and a polypus had been removed from the meatus a few weeks previously. On the 5th of November a swelling developed behind the right ear, and a curved incision was made through the periosteum down to the bone by his medical attendant. On admission, his temperature was 100·2°, pulse 104, and respiration 20. The same evening the previous incision was enlarged and converted into a T-shaped one by a horizontal incision carried backwards from its mid-point; the periosteum was freely detached both forwards and backwards, when a fistulous opening was seen leading into the antrum. The cortex around this was freely removed, exposing a cavity containing pus, which, as it pulsated synchronously with the pulse, suggested that an extra-dural abscess was present. After the antrum and mastoid cells had been freely opened it was found that the inner wall of the abscess cavity was formed by granulating dura mater, lying over the descending portion of the lateral sinus in the posterior fossa: in fact, a perisinuous abscess was present. The bone around the granulating area of dura mater, and the posterior aspect of the petrous portion of the temporal bone, was freely removed until healthy dura mater was reached in every direction. In doing this the superior petrosal sinus was opened and plugged, but the lateral sinus contained fluid blood and was left intact. The radical mastoid operation was completed in the usual manner, and the whole wound was packed. The patient's temperature gradually fell to normal, and his pulse varied between 72 and 80. On November 10th he began to complain of vertigo, and on the 14th he vomited. As the vertigo was most marked when his ear was being syringed or dressed, it was not thought to be of serious importance. On November 16th Mr. Ormond examined his eyes and found there was no optic neuritis. On the 18th preparations were made for skin grafting the mastoid wound, but on attempting to walk to the operating theatre the patient became so giddy as to need support. It was also noticed that he had become considerably thinner during the past week, and had developed horizontal nystagmus. His cerebration was slower than usual and his speech sluggish. For the past ten days his temperature had been subnormal, but his pulse had varied between 96 and 72. The diagnosis of brain abscess having been made, the patient was anæsthetised, and the dura mater behind the lateral sinus was transversely incised over the site of the old extradural abscess. When the knife had passed into the cerebellum for about half an inch pus escaped, and on dilating the opening with forceps about one and a half ounces of pus was evacuated. This on bacteriological cultivation gave rise to a growth of a member of the mesentericus group, but no pathogenic organism could be isolated. On November 23rd there was still slight horizontal

nystagmus, but none of the other intracranial symptoms had been noticeable since the operation.   The discharge of pus from the abscess cavity gradually decreased, and on December 20th the patient was anæsthetised, and the edges of the large post-auricular wound were brought together with sutures. He was discharged from the hospital on January 8th, 1908.

CASE 4.—Jane R., æt. 60, was admitted into Ruth ward under my care on November 14th, 1907, suffering from polypi and chronic suppuration in the upper part of the nose, with symptoms of disease of the frontal cells.   She had had polypi removed on two occasions about a year previously.

November 15th, 1907.   Operation.—Incisions were made on either side along the eyebrows, the frontal sinuses thoroughly opened and granulation tissue scraped out.   The anterior ethmoidal cells were much involved and their walls were thinned and carious ; much diseased bone was removed with gouge and forceps, including part of the cribriform plate and the crista galli, so that the dura mater was widely exposed; the wounds were sutured and two drains were inserted downwards into the nose, via the infundibula, which remained *in situ* for three days.   After their removal the wound was carefully syringed out daily, gauze drains being inserted, which were omitted on November 25th.   There was a slight discharge of muco-pus from the frontal sinus up to December 8th, but this had ceased by December 11th, when the patient was discharged from the hospital with the wound practically healed.   She was re-admitted on December 18th in a drowsy condition, the temperature being 97°, the pulse 64, cerebration slow, speech sluggish, and her mental condition much altered ; the old frontal headache has returned and is now most intense.   She was apathetic and depressed, and seemed to take no interest in her surroundings.   Her temperature remained subnormal, but on December 20th her pulse fell to 56.   Her mental condition has now slightly improved, and she seemed to be more intelligent.   Mr. Steward kindly saw the patient at my request, and found the right side of the nose perfectly clean and healthy, but he found pus high up on the left side of the nose, and in the presence of cerebral symptoms thought that an abscess in the left frontal lobe was probable.   The same day, under an anæsthetic, the left frontal sinus was opened up again, and after the bone forming its posterior wall had been removed, the dura mater exposed at the previous operation was freely incised.   The introduction of forceps into the left frontal lobe resulted in the evacuation of an ounce and a half of very foul-smelling pus.   A drainage tube was inserted and the wound packed. The patient never regained consciousness, and died the same evening. At the autopsy the abscess cavity was seen to extend from the orbital surface of the frontal lobe nearly to the anterior horn of the lateral ventricles. The brain, for a distance of two inches beyond the periphery of the abscess, was acutely inflamed and softened.

CASE 5.—William W., æt. 51, was admitted into Lazarus ward under Mr. Lane on January 18th, 1908, suffering from loss of speech.   He had suffered from left otorrhœa for thirty years, with frequent attacks of headache and vomiting.   For these he had been occasionally treated at another London hospital.   On January 16th, when commencing his round as a milk-man, he became giddy, but in a few minutes recovered sufficiently to

continue his occupation. Later in the day he suddenly lost power in his legs and was taken home, where he remained in bed until admission to the hospital. On admission, his pulse rate was 52, temperature 98·4° F., and respirations 18. He was in a very dazed and apathetic condition. He appeared gradually to understand what was said to him, but could only talk with difficulty, and even then was hardly intelligible. A diagnosis of temporo-sphenoidal abscess was made, and immediate operation was undertaken by me. Left antrectomy was performed, but no active mischief was found in the antrum or in the mastoid process. The tegmen antri appeared normal, but so strongly did the symptoms point to the presence of an abscess that the bone in this situation was freely removed until healthy dura mater was exposed. On incising the dura mater and exploring the temporo-sphenoidal lobe, both with forceps and with the finger, no abscess was detected, but the brain substance immediately underneath the cortex seemed to be unduly friable and soft over an area about an inch in diameter (*see* 1 in diagram). A drainage tube was inserted into this cavity, and the patient returned to bed. On January 24th it was noted that his mental condition was clearer, and he understood what was said to him more quickly than formerly, but still complained of headache and sleeplessness. The temperature was usually subnormal, and the pulse ranged from 60 to 84. On the 31st Mr. Eason examined the patient, but found no optic neuritis. A good deal of pus continued to drain away from the post-auricular wound. On February 14th it was noticed that the patient's condition was gradually getting worse : for the past three days a gradually increasing right-sided facial paralysis of the supra-nuclear type had been observed, and was now well marked, affecting all the muscles of the face below the eye completely, but the eyelids hardly at all. The difficulty in speech had again relapsed, and it was now extremely difficult to understand what the patient said. Dr. French saw the patient on this day, and was of opinion that the symptoms were due to an abscess in the lower and front part of the left Rolandic area. On February 17th, as the patient continued in the same condition, he was seen by Dr. Pitt and Dr. French. The patient could transcribe accurately, and could also write down correctly the names of articles shown to him, but he could not articulate any words distinctly, and talked a sort of unintelligible jargon. He knew his relatives and others around him, and wrote down their names quickly and accurately. He also correctly copied a paragraph from a newspaper. Dr. Pitt agreed with Dr. French in the diagnosis of cerebral abscess involving the speech centre in the left inferior frontal convolution. On February 20th the condition was unaltered. The temperature was subnormal, and the pulse varied between 60 and 80. The patient was anæsthetised, and, after the fissure of Rolando had been marked out upon the scalp, a large flap was turned downwards, so as to expose the lower half of the motor area. An elliptical area of bone was removed with a gouge and mallet from the anterior and lower part of the left parietal bone, adjacent to the squamous portion of the temporal bone. This was so planned as to be bisected by the Rolandic fissure above and to extend below beyond the Sylvian fissure (see diagram). An exploring needle was then introduced in several directions, but no pus could be withdrawn. The dura mater was then incised, in doing which the anterior branch of the middle meningeal artery was divided and ligatured. A finger was then introduced in a downward and forward direction, when pus escaped, and on enlarging the wound

Portion of skull removed

Abscess opened   Necrotic area drained
at 2ⁿᵈ operation   at 1ˢᵗ operation

—·—·—·—·—·— Cerebral fissures
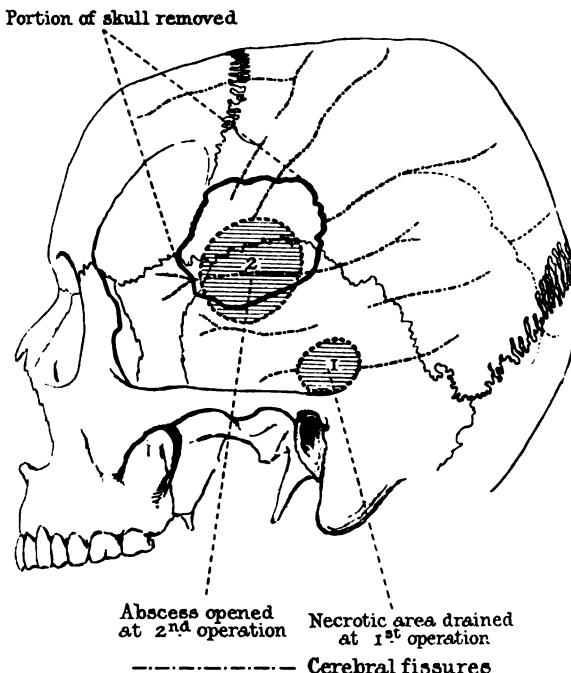
with forceps about two ounces of pus were evacuated. It was thought that the abscess was in the temporo-sphenoidal lobe, immediately below the Sylvian fissure. On introducing one forefinger into this cavity and the other forefinger into the cavity resulting from the first operation, a layer about half an inch thick of brain was found to intervene, and after this had been perforated with sinus forceps a long drainage tube was introduced from the parietal wound through the abscess cavity and drawn downwards through the temporo-sphenoidal lobe, so as to project at the old post-auricular wound. On February 24th it was noted that the patient was able to say that he felt quite well, only he could not talk properly. After this his speech gradually improved, and he got up on March 3rd. Cultivations from the pus evacuated at the second operation remained sterile after three days' incubation at 37° C. On March 24th his condition was still improving. His speech was almost normal at times, especially in the morning, but at other times he could only be understood with difficulty. The facial paralysis was gradually recovering, but the muscles on the right side did not react so well as those on the left side of the face. He left the hospital on April 14th, when both wounds were closed. Dr. Pitt saw the patient with me during June, 1908, when there was no noticeable facial paralysis, and speech was almost normal. He was then able to carry out his usual occupation.

CASE 6.—Sidney W., æt. 8, was admitted into John ward, under Dr. Hertz, on April 4th, 1908, suffering from headache, sickness and drowsiness. In 1903 he had discharge from the right ear, which cleared up on treatment. Four

weeks before admission the discharge recurred, and a week later he was seized with sickness. On March 25th he became worse, the sickness increased, and he was continually drowsy. On admission his pulse was 66, his temperature 96·5°, and his respirations 18. He was well nourished, had a far-away look, and constantly cried out in a high-pitched voice. There was ptosis of the right upper lid, and the right internal rectus was paralysed. The right pupil was larger than the left, and there was well-marked right optic neuritis. The reflexes were normal. The patient complained of considerable headache, which was more marked on the right than on the left side of the skull. Under an anæsthetic the right antrum was explored, and found to be filled with cholesteatoma. The dura mater covering the lateral sinus was exposed and found to be healthy, but over the roof of the antrum there was considerable deficiency of the bone, exposing granulating dura mater. The adjacent bone was removed with forceps, and the temporo-sphenoidal lobe was explored with a scalpel, when an ounce of stinking foul greenish pus was evacuated. The radical mastoid operation was completed, and a drainage tube having been inserted into the abscess cavity the wound was packed with gauze. Cultures from the pus showed the presence of Friedländer's bacillus. No organism was found in a specimen of cerebro-spinal fluid obtained by lumbar puncture. During the next few days the patient's condition improved. The headache was relieved and the ptosis and strabismus became less noticeable. The pulse was at first rapid, but gradually fell to 80. On April 20th there was again some ptosis, and the child complained of the return of headache. There was a small hernia cerebri. As it was thought that the abscess cavity was not draining properly, the patient was again anæsthetised on April 22nd, and on dilating the sinus with dressing forceps more pus was evacuated. This relieved the headache, and the ptosis and strabismus disappeared. The post-auricular wound was slowly healing by granulation, when on May 25th he was transferred to Barnabas Ward, as his ear still required attention. On May 29th he was sick in the morning, complained of headache and loss of appetite, and wished to return to bed. On the wound being dressed, and the packing removed, no pus escaped from the sinus, nor did the introduction of a probe or dressing forceps cause any to escape. The wide drainage tube was then re-introduced in place of the gauze, and immediately about one and a half ounces of thick greenish pus escaped, and this was followed within a few minutes by complete relief of the headache ; for several days the right pupil was dilated, and the ptosis recurred ; double optic neuritis was noticed. His condition continued to improve until June 17th, when, while sitting on the colonnade railing, he felt giddy, and on falling had convulsive movements of the right arm, right leg and left arm. After this he remained in bed for a few days ; the post-auricular wound continued to granulate satisfactorily until his discharge on the 6th August. After leaving the hospital he was repeatedly seen in the Out-Patient Department ; his condition varied considerably, and the sinus behind the ear did not heal. As I feared further retention of pus in the old abscess cavity, he was re-admitted on November 12th, 1908 ; the next morning under an anæsthetic the post-auricular sinus was enlarged and the track dilated, when about two drams of pus escaped from the former cavity. In order to attempt better drainage much of the conchal cartilage was cut away and the external auditory meatus widened, a large rubber tube

being passed through it into the abscess cavity; the posterior incision was closed. For several days his temperature remained down, but on the 18th reached 102°F., and the post-auricular wound was suppurating; a sinus appeared and the temperature soon fell to normal, but a gradually increasing hernia appeared behind the ear; on November 24th Mr. Eason found acute optic neuritis. At this time the drainage tube went in 2½ inches, but on December 7th it could only pass in 1¼ inches through the meatus, so it was re-inserted behind the ear. On December 10th the optic neuritis had nearly subsided, but on the 14th the temperature rose to 102° and pulse to 142, and the patient complained of great headache. Under an anæsthetic the temporo-sphenoidal lobe was explored, but no pus was found; the hernia was shaved off and the wound packed with gauze; the headache improved and pulse and temperature fell, but on the 23rd paresis of the left side of the face was noticed; it was of the supra-nuclear type and was confined to the muscles around the mouth. At Xmas patient got up every day and his appetite was good, temperature 98–99°F., pulse 90–100. During January the general condition improved and discharge was abundant, the temperature ranged around normal, but on February 2nd one of his periodical attacks of headache and pyrexia started, and nearly every day this month the temperature reached 102°F. at some time in the twenty-four hours, this was associated with an increase in pulse rate and a feeling of malaise. On March 10th cultivations from the sinus showed the presence of bacillus coli communis; on the 18th he had an injection of bacillus coli communis vaccine (5,000,000), and this was repeated on the 22nd; the dresser notes that the discharge is more abundant and thinner. The general range of his temperature is lower (98–101°), but the pulse rate has increased; on the 27th the temperature reached 102·4°F., the pulse rate 136; next day it was lower, and his general condition was as usual. He died suddenly the following morning at 2 a.m. At the autopsy there was some opacity of the meninges, the right temporo-sphenoidal lobe was soft and contained a large abscess cavity full of pus; it extended to, but did not involve, the occipital lobe.

CASE 7.—Winifred C., æt. 9, was admitted into Miriam ward, under Dr. Pitt, on October 3rd, 1908, for unconsciousness of twenty hours' duration. Her parents said that ever since measles at five years of age she had suffered from intermittent bilateral middle ear suppuration. Her tonsils and adenoids were removed in 1907, when the parents were told that both drums were perforated. When discharge occurred it was always controlled by syringing, but for the previous six months this had not been necessary. On September 20th, after a journey, she complained of left earache with headache, and was twice sick; the next day the sickness continued; it was described as occurring suddenly and without nausea. She continued in the same state, and the doctor was called in on the 22nd. On the 25th she had a rigor, and these recurred every morning and evening; her temperature reached 104° and sickness did not abate; on the 26th the headache was more intense. Her parents did not appreciate her grave condition, and refused the doctor's offer to send her to hospital. About this time her speech became slow, and it was difficult to get her to answer questions. On October 2nd her head was turned to the right, and there was conjugate deviation of both eyes to the right; she gradually became comatose, and her parents consented to her admission.

Condition on admission at 3.30 p.m.: pulse, 98; temperature, 99°; she is unconscious and lies curled up on her right side: the eyes are turned to the right; there is no optic neuritis. The right membrane is thickened, scarred and retracted, the left meatus is full of offensive pus, and the left mastoid is tender, but not swollen. The knee-jerks are exaggerated and the plantar jerk is extensor. Dr. Pitt diagnosed lateral sinus thrombosis with left cerebellar abscess, because of the conjugate deviation of the eyes to the right. At 6.45 p.m. I saw her and hesitated to operate owing to her apparently hopeless condition; as, however, it gave her her only chance, I made a crescentic incision behind the left ear and evacuated a subperiosteal abscess; at the bottom of the cavity pus was seen oozing through the foramen for the mastoid emissary vein, and on freely removing bone around this an extensive extradural abscess was laid open. Running across the floor of the extradural abscess was the lateral sinus, filled with disintegrating thrombus. The antrum was opened, and between it and the infected contents of the posterior fossa was a definite track of carious septic bone; the lateral sinus was cleaned out until fluid blood escaped at both ends, when gauze plugs were inserted. Owing to the necrotic state of the dura mater it was thought probable that infection had spread through it, so an incision was made in it within the concavity of the genu of the sinus, *i.e.*, behind it. An acute cerebellar abscess was at once entered, into which a rubber tube was fixed; the whole wound was packed. After the operation the pulse-rate was 180. The patient was given five minims of the inj. strych. hypoderm. infantum. Later in the evening her temperature was 105° and pulse 190; continuous rectal saline was given, and the next morning both had fallen; she was fed chiefly with nutrient enemata. Towards evening she became more conscious and was able to swallow milk : she breathed with difficulty, and made a rattling noise owing to mucus in her trachea. On October 5th acute bedsores developed on the left heel and sacrum. Her temperature was subnormal. On the 6th she was more conscious and recognised her father; sharp rales could be detected over the back of both sides of the chest. On the 7th her condition was still better, and the conjugate deviation of the eyes was not so marked, but she could not move the eyes to the left beyond the midline; the rotation of the head was less marked; the pupils were equal and dilated. On the 8th she was irritable, answered questions coherently, complained of headache and pains in the chest; there was a pleuritic rub over the left base; the sacral bedsore was breaking down. On the 10th there was a slight hernia of the cerebellum; Kernig's sign was positive; temperature 99° F. October 12th, patient was not so well, pulse 120–150, temperature 98–101·5° F. Cultures from the wound at the operation show bacillus coli communis and staphylococcus aureus. On the 16th bronchial breathing and rales extended on the right side up to the angle of the scapula. On October 19th her breath was very foul, pyrexia remittent and pulse very rapid, and diarrhœa was troublesome. On the 21st staphylococcic vaccine was injected; on the 23rd the patient was worse, colour very bad. pulse 180, small and wiry; the right chest was explored with a negative result. She died early on the morning of October 24th. An autopsy was refused by her parents.

CASE 8.—Ernest A., æt. 17, was sent to my Out-patients on December 1st, 1908, by Dr. F. W. Wilson, for continuous discharge from the right ear

with headache and vomiting; he had been operated on at Guy's in 1903 for a
"mastoid abscess." As the swelling recurred three months later he was again
admitted and a further operation carried out. The discharge continued, how-
ever, and in November, 1908, pain with tenderness and swelling over the right
mastoid recurred and a superficial abscess was opened in the Front Surgery;
during October and November he had suffered periodically from vomiting,
headache and giddiness. On examination of the right ear there was much
purulent discharge; an incomplete radical mastoid had been done and the
middle ear was filled with granulation tissue; a radical mastoid was recom-
mended and his name taken for admission, but on December 4th his doctor
sent him up again because of continuous vomiting for three days, and he was
admitted into Barnabas ward. On admission he was very drowsy, temperature
99°, pulse 108; he suffered from extreme headache; he was anæsthetised and
the usual crescentic incision made behind the right ear; the cavity resulting
from the previous operations was freely opened and found full of foul-
smelling cholesteatoma. After curetting away granulation tissue from the
antrum and middle ear a fistulous track was seen leading into the external
semicircular canal; superior vestibulotomy was done, much carious bone
being removed with gouge and spoon until the facial nerve was entirely
isolated for a distance of half an inch; the post-auricular wound was
sutured with drainage of the vestibule through the meatus. On the 5th the
dresser notes, "There is no sign of facial paralysis, although during the
operation the face twitched repeatedly," the patient was drowsy, but his
headache was less; on the 7th he was more drowsy, but the headache was
less and the vomiting had considerably decreased; there was no optic neuritis;
on the suspicion of brain abscess, as with increasing coma his temperature
had fallen to 97·6° and the pulse-rate to 70, Dr. Fawcett was asked to see
him. He agreed with my suspicions and inclined to locate it in the
cerebellum owing to the tendency to Cheyne-Stokes respiration, falling
pulse-rate, coma and general aspect. I therefore operated and removed the
bone widely around the large mastoid wound, but at no spot could I
find any carious focus leading to the dura mater; where the antro-tympanic
roof had been removed the temporo-sphenoidal lobe was exposed and, after
incising the dura, was explored with knife and forceps, but though the brain
bulged no pus was found. The right lateral cerebellar lobe was similarly
dealt with within the area where the postero-internal antral wall had been
removed. The dura antero-internal to the genu of the lateral sinus was
incised, when about two ounces of thin pus was evacuated and a drainage
tube inserted. On the 8th the patient was no better, but towards evening
somewhat regained consciousness, temperature 99·2°, pulse 100. He died
quietly the next morning. At the autopsy the skull disclosed two holes, the
upper half an inch in diameter leading to the middle fossa, the lower leading
into the posterior fossa. The brain showed no meningitis, there was a hole
half an inch in diameter and a quarter of an inch deep in the temporo-
sphenoidal lobe corresponding to the upper hole in the skull; around this the
brain substance was softened. Corresponding to the lower hole in the skull
was a recent ragged abscess cavity in the lateral cerebellar lobe; it was quite
superficial, the brain around was softened, and a probe passed with little
resistance from the abscess cavity into the 4th ventricle, but the latter
contained no pus. The meninges and lateral sinus were normal; there was
no obvious track of extension from the ear to the cerebellar abscess.

CASE 9.—Wm. B., æt. 24, was admitted on June 2nd, 1909, under my care, for delirium and left hemiplegia. His relatives stated that for eight or nine years he had suffered from right otorrhœa with intermittent attacks of headache. On May 29th the ear was discharging, and he complained of severe headache; he vomited several times. On June 2nd he came up to the Front Surgery and was treated as an out-patient, but a few hours later he became worse and lost consciousness; he was again brought up to Guy's and admitted late the same evening. Condition on admission: Temperature 96°, pulse 84. The patient was unconscious, with some delirium; there was paralysis of the left arm and leg and of the external rectus of the left eye; there was no optic neuritis, the abdomen was somewhat retracted. There was no discharge from the right ear, but on examination a large reniform perforation was seen, through which the granulating inner wall of the middle ear was exposed. It was not possible to carry out the operation without an anæsthetic, so at 1.30 a.m. chloroform was administered, and the right antrum was opened and found to be filled with cholesteatoma. The different steps in the performance of a radical mastoid operation were then carried out, after which the roof of the antro-tympanic cavity was freely removed with gouges and Jansen's cutting forceps. The exposed dura mater covering the temporo-sphenoidal lobe bulged slightly, but on incising it and exploring the subjacent brain with forceps and the index finger no pus was discovered. The dura mater lining the posterior fossa was then exposed by removing more bone behind the antrum, when antero-internal to the genu of the lateral sinus an area was found thickened and covered with granulations. An incision was therefore made through this patch, when about 2 drachms of thick pus escaped from the right lateral lobe of the cerebellum. A drainage tube was inserted and secured in position with a safety pin. It was felt that this small abscess could not account for all his symptoms, and that suppurative meningitis must also be present. The next morning his temperature was 100·2°, and pulse 88. He was still comatose, but able to move the left arm. On the 4th his pulse rose to 160 and his temperature to 105·2° F., and he died at 9 p.m. At the autopsy there was suppurative meningitis over the whole of the base of the brain.

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CASE 10.—Mrs. W., æt. 27, was seen by me on September 16th, 1909, with Dr. R. W. Mayston of Erith, for vomiting and excruciating headache; her pain was so great that she was unable to give the history of her ear trouble, but her relations stated that she had right chronic middle ear suppuration as a child, though there had been no trouble since that time until a month ago, when after some acute pain the right ear began to discharge. Becoming severely ill in Panama she left for England, and was so bad on reaching Barbados that the ship's doctor asked for a consultation with another doctor from the island, as he thought it dangerous for her to go any further, as " an operation was urgently necessary." However, she was allowed to come on, and with many temporary improvements and relapses, arrived home; she had emaciated considerably since the illness began, throughout which she had excruciating right parietal, frontal and occipital headache, its position varying at different times; her temperature has ranged between 101° and 99°; and her pulse between 110 and 80. She had vomited several times on the voyage, and rather more often since arriving in England; she had one

shiver early in the illness, and a more marked one on September 15th. Her cerebration was normal, though she answered questions slowly and with hesitation, owing to the increase of pain, which any effort seemed to produce, and for the same reason appeared sleepy, though there was no real drowsiness ; there was no optic neuritis or retraction of the head, her knee-jerks were brisk, there was no Kernig's sign ; temperature 99° ; pulse 80. The left membrane was normal, but the right showed an old posterior perforation exuding foul-smelling pus. In our opinion she had an acute intra-cranial abscess secondary to chronic right middle ear suppuration, and in the absence of any definite localising symptoms the temporo-sphenoidal lobe seemed its most likely situation. Operation was undertaken some seven hours later, by which time her pulse had fallen to 60 ; the antrum was opened and contained a little thick pus ; the roof of the antro-tympanic cavity, much thinned and carious, was freely removed, exposing an inflamed granulating area of dura in the middle fossa. On incising the dura and subjacent cortex no pus was found, so the bone-wound was enlarged backwards to expose the posterior fossa. At an earlier stage in the operation I had noted that the genu of the lateral sinus was placed abnormally far forwards, and in removing more bone the sinus was accidentally opened with Jansen's bone forceps, probably by tearing away an emissary vein at its entrance to the sinus. Slight delay was caused by removing more bone over the outer wall of the sinus, when it was easily plugged with gauze ; on gouging away the posterior surface and upper border of the petrous antero-internal to the sinus, the posterior part of the above-mentioned area of granulating dura was exposed, and here the inflammatory changes were more marked than in the middle fossa. A scalpel was passed at the centre of this area through the dura and subjacent cerebellar cortex, when about 4 drams of stinking thin pus came out. A rubber drainage tube was inserted and the whole wound was packed with gauze. The next morning the patient had lost all her headache, her pulse had risen to 90. During the next week she gained flesh rapidly and resumed a good colour in place of her previous pallor ; the small gauze plug in the sinus was removed on the 5th day, when no bleeding resulted, and the drainage tube in the cerebellum was removed and replaced. On September 24th she had some headache and vomiting ; these were relieved by reintroducing the drainage tube. The improvement in mental vigour, interest in her surroundings and in general health continued, and were phenomenal, and there had been no more vomiting or other untoward symptoms when she left the hospital on October 2nd.

REMARKS.—The. above ten cases of brain abscess were typical in that there was present in each patient a chronic suppurating focus, which in each case suggested itself as the possible cause of such a condition. In nine of them the ear was the obvious primary focus, and in the tenth the presence of nasal polypi and chronic nasal discharge· pointed to the nose as the initial lesion. In one of the ear cases (case 2), however,

it must be borne in mind that the temporo-sphenoidal abscess was distinctly traumatic in origin, in that inoculation of the brain substance took place during the course of a comparatively slight operation.

Pitt (Goulstonian Lectures, *Brit. Med. Journ.*, 1890, vol. i., p. 643, *et seq.*), in abstracting the reports of 9,000 autopsies, found fifty-six cases of cerebral abscess, of which in eighteen cases, or one-third of the total number, the abscess was caused by disease of the temporal bone, and in eight more other bones of the cranium were the seat of the primary affection (41 per cent. in all).

Most of my cases may be regarded as passing through what is called the " latent stage" of cerebral abscess, when slight headache, depression, malaise, and a slight rise of temperature in the evening, are frequently the only general symptoms to be found, and these are so liable to be falsely interpreted as due to other fibrile conditions in their initial stages. While under observation several of the cases passed from this stage into the " manifest" stage of abscess. I was unfortunate in cases 7 and 9 to be called upon to deal with cases which had passed into the " terminal " period, when marked symptoms suggested that the abscess had ruptured into the ventricles or had invaded the meninges.

The " general " symptoms of brain abscess are not usually, nor were they in these cases, of great diagnostic value, but a sense of weakness, with slight pyrexia, on several occasions led us to the conclusion that the abscess in case 6 was not being satis-factorily drained, and the establishment of free drainage rapidly led to the temporary disappearance of these symptoms. Also in cases 3 and 10 the rapid emaciation was a great help in promptly arriving at a diagnosis. After slight pyrexia in the initial stage, the temperature is in many cases subnormal in the " latent " stage of abscess, uncomplicated either by acute inflammation of the primarily affected bone or by other intracranial mischief such as meningitis or sinus thrombosis; this was typical in cases 3, 4, 5, 6, and 8,

In each of the above cases " pressure " symptoms were well
marked, and of these the most important is undoubtedly head-
ache. It was one of the most distressing symptoms in cases 1, 2, 4,
6, 7, 8, 9, and 10, and was slightly marked in case 5; in contrast
to which it is especially worth notice that in case 3 headache was
practically absent throughout the whole illness, both during
and after which, even on direct inquiry, the patient confidently
stated that he had no pain worth complaining of. In this case
the abscess was evidently of fairly recent origin, and as the
symptoms pointing to its presence were only noticeable for a
week, and as at a previous operation, undertaken twelve days before
the cerebellar abscess was evacuated, the dura mater had been
freely exposed, at first sight the idea suggests itself that the free
removal of bone at the first operation may account for the absence
of this symptom. If this is a satisfactory explanation it is
opposed to the fact that headache was present in case 2, in which
a similar sequence of events took place, and also to the fact that
removal of bone alone does not relieve the headache met with in
cases of cerebral tumour. Except in cases 4 and 6, the position
of the headache had no localising value, nor was its severity at
all proportionate to the size or rapidity of formation of the
abscess.

Vomiting was present in the initial stage in cases 1 and 9, and
was continuous in cases 6, 7, 8, and 10. In neither case had its
incidence any relation to diet or meals, so that its presence did
not confuse the diagnosis by suggesting that it was due to the
presence of an abdominal lesion.

The giddiness and staggering gait, so typical of cerebellar
lesions, were only met with in case 3, in which the diagnosis was
easier than in any of the other cerebellar cases (7, 8, 9, and 10).

Drowsiness was well marked in cases 2, 5, 6, and 8, while the
onset of symptoms in case 1 was heralded by actual loss of
consciousness. Cases 7 and 9 were both unconscious on admission.
That most valuable combination of symptoms, *e.g.*, slow cerebra-
tion, long latent period, lethargy, sluggish speech, defective
attention, was marked in many of the cases, and went far in case
5 to enable us to come to an accurate diagnosis. These symptoms,

in association with a slow pulse, especially when, during a few hours' observation, the pulse rate continuously falls, have been in my experience the most valuable indications that an abscess is present somewhere in the brain.

Slowing of the pulse rate was met with in cases 1, 4, 8, and 10. This symptom, indicative of increased intra-cranial tension, usually disappears immediately on evacuation of the abscess.

Optic neuritis was present in cases 1 and 2 on both sides. It was definitely absent in cases 3, 4, and 10, and in case 6 was unilateral, being limited to the side of the abscess. It might be urged that cases 3, 8, and 9 were so acute that optic neuritis was not likely to be present, but its absence in cases 5 and 7 cannot be similarly explained away. In fact, these were typically cases in which its presence might have been expected. Therefore these two cases coincide with my impression that in cases of intracranial abscess optic neuritis is extremely erratic in its occurrence, and, as a further point, I should like to insist that it will often progress after the lesion producing it, *e.g.*, extradural abscess, has been radically dealt with, for which reason I regard it as of very little value either in diagnosis or prognosis.

The " localizing " symptoms varied in each case. In case 5, aphasia, with crossed seventh nerve paralysis of the supranuclear type, indicating that the centres occupying the lowest part of the left motor area were affected, was sufficient to lead me to the site of the abscess. In case 1, with a left-sided temporo-sphenoidal abscess, there was paralysis of the left sixth nerve, producing homonymous diplopia. In case 2 there was partial paralysis of the third nerve, and in case 6 there was paralysis of the levator palpebræ superioris and the internal rectus, with dilatation of the pupil : in both the last-mentioned cases the paralysis was on the same side as the temporo-sphenoidal abscess. In case 7 the conjugate deviation of the eyes to the right suggested a left cerebellar abscess. The paralysis of the left sixth nerve in case 9 was no doubt due to the meningitis rather than to the small cerebellar abscess.

The occurrence of ocular paralysis in five out of the ten cases has been my chief reason for putting them together in this

paper. Körner (" Die Otitischen Erkrankungen des Hirns, der Hirnhaüte und der Blutleiter, 1908, p. 160–1) points out that the oculomotor nerve of the affected side is that usually involved by a temporo-sphenoidal abscess of any considerable size. The paralysis is seldom complete, being usually limited to the production of ptosis and dilatation of the pupil. In case 2 the limitation of the paresis to the extrinsic ocular muscles led Mr. Eason to suggest a provisional diagnosis of abscess in the region of the corpora quadrigemina, because he argued that the nucleus must be involved. It is interesting here to quote some remarks by Körner (*loc. cit. supra*), in which he says, " Most Neurologists and Ophthalmologists take for granted that a lesion which affects the trunk of the oculomotor nerve causes a complete paralysis of the nerve, and that a partial paralysis of the same is of nuclear origin. How can it be that in the presence of an abscess in the temporo-sphenoidal lobe injury to the oculomotor nucleus is almost constant ? Must not such a lesion partially paralyse *both* oculomotor nerves ? " He concludes with an explanation of the above clinical difficulty by suggesting that the fibres which control the pupil and the elevator of the upper eyelid, as they run in the nerve-trunk, are more vulnerable than the other fibres of this nerve. It is probably right to regard the presence of unilateral oculomotor paralysis as having no exact localising value except that it suggests, when associated with other symptoms of abscess, that the lesion is somewhere in the temporo-sphenoidal lobe of the same side as the eye affected.

Most of my cases showed no " distant pressure effects," such as crossed hemiplegia due to temporo-sphenoidal abscess ; these are no doubt due to a spreading inflammation beyond the limits of the abscess. In case 5 the crossed supranuclear facial paralysis and aphasia were probably of this nature, for as at the operation the abscess did not directly involve the motor area, and there was subsequent complete recovery both of facial movements and of speech, the assumption that there had been a gross lesion of these centres is untenable. In case 3 the abscess in the lateral cerebellar lobe produced the ataxy and giddiness typical of this lesion, which are due to pressure on the vermis.

The *diagnosis* of brain abscess varied considerably in difficulty in these ten cases. In case 1 the combination of symptoms was typical, and as at the first operation there was found to be destruction of bone down to the dura mater in the middle fossa, and there was pachymeningitis externa in this position, the seat of the abscess, if any were present, was almost certain. In case 2, though the peculiarity of the ocular paralysis was at first sight confusing, the known injury to the temporo-sphenoidal lobe at the first operation absolutely localised the abscess to this position. The remarks which I have just made about case 1 apply equally to case 3; for here, while the lateral sinus was apparently healthy, when the symptoms of abscess became marked it was naturally localised to the lateral cerebellar lobe underneath the area of granulating dura mater, even had not the symptoms of giddiness, nystagmus and ataxy, so typical of cere-bellar abscess, been at hand. In case 4 I was in some doubt as to the localisation of the abscess, or, in fact, as to whether an abscess were present. But the suspicion that the left frontal lobe was involved, based upon the marked mental change character-istic of left frontal lobe abscess, was confirmed when Mr. Steward found pus in the upper part of the left nasal cavity. When advocating immediate operation on case 5, so typical were his symptoms that I felt positive that a temporo-sphenoidal abscess would be found. This view was considerably shaken when the bony roof of the antrum and tympanum was found to be normal, and seemed to be certainly negatived after a thorough exploration of the adjacent portion of the temporo-sphenoidal lobe had failed to evacuate any abscess, for even after the operation I could not convince myself that the small necrotic area found in the temporo-sphenoidal lobe was sufficient to have produced the symptoms. Subsequently the diagnosis of abscess in the upper portion of the temporo-sphenoidal lobe was not obvious—to me at least—and it was not until a month later that I felt justified in a further exploratory operation, even though a week previously Dr. Pitt and Dr. French had given me their opinion that such an abscess was present.

The remarks I have made on cases 1 and 3 equally apply to case 6. This boy clearly had an acute intracranial lesion demanding immediate operation. During the course of this operation it was found that the bone above the antrum had been destroyed, and that the dura mater in this position was exposed and granulating. There could be no question that his symptoms were too severe to have been produced entirely by this amount of external pachymeningitis, and therefore it was only natural to explore the subjacent temporo-sphenoidal lobe.

Owing to the associated complications in cases 7 and 9, they are of little value in discussing the diagnostic importance of symptoms. In case 8 the presence of an abscess was fairly certain owing to the increase of " general symptoms," and the labyrinthine involvement pointed to its localisation in the cerebellum.

My observations on cases 1, 3 and 6 also apply to case 10. It was clear she had a brain abscess ; its exact locality could only be decided by following the disease to its termination.

The *operative procedures* in all these cases were based on certain pathological facts which I have already several times touched upon, but which are, in my opinion, so important that they can be summarised here with advantage. Though the subsequent remarks refer particularly to abscesses in the temporo-sphenoidal or cerebellar lobes resulting from disease of the tympanum and adjacent cavities, they are, as far as my experience goes, equally true of abscess in the frontal lobe resulting from suppuration in the nose and its adnexa.

Dealing therefore for a few minutes solely with brain abscess of otitic origin, the following premises can be absolutely relied upon :—

a. Brain abscess is much more commonly the result of chronic suppuration than of acute. Grünert, quoted by Schwartze (Handb. der Ohrenheilkunde, II., 849), is of opinion, from statistics based on a large number of reported cases, that in 91 per cent. of abscesses the cause is chronic, while in only 9 per cent. is it acute suppuration.

b. In an overwhelming majority of cases brain abscess is associated with active bone disease; only rarely is it due to uncomplicated disease of the lining mucosa of the cavities within the bone. Frequently will there be extensive destruction with necrosis, or erosion through the action of cholesteatoma.

c. Such bone disease almost always extends to the dura mater, which itself is involved. Körner notes that in forty cases of otitic brain abscess the bone was thirty-seven times destroyed to the dura; in one case the bone was diseased, but the dura was not exposed, and only in two cases was the bone adjacent to the abscess cavity found to be healthy. I cannot do better than emphasise this, to my mind, the most important of all patholo- gical facts bearing upon the operative treatment of brain abscess by quoting Körner (*Loc. cit. supra,* p. 18), when he says, " We have, before everything, to reckon with the important and still not always sufficiently appreciated fact that in almost all brain lesions of aural origin the bone is found diseased down to the dura."

d. That the dura will be found to be externally inflamed and granulating, but that extradural abscess is unusual. When a subjacent brain abscess is present the diseased dura is almost always adherent to the underlying structures, and here there is usually a thin layer of brain substance, itself diseased, between the abscess and the affected dura.

e. As a summary of the above, we may deduce a clinical fact of the greatest importance, that such brain abscesses occur in exceedingly close proximity to the primary disease, *e.g.,* ear or nose, and to the underlying affected bone.

From a perusal of the notes of my ten cases, it will be seen that in eight of them all the above clinical axioms were accurately upheld. In case 5 only was there no evidence of a gross bone lesion, the dura mater was not involved, and the abscess found at the second operation was not in proximity to the causative lesion. In case 8 the bone disease had involved the labyrinth, but this focus was not obviously connected with the cerebellar abscess.

Operative treatment.—I do not propose here to detail the various procedures that may be called for in any operation for brain abscess, as the methods which in my opinion are the best are sufficiently drawn attention to in the notes of the individual cases. I should like, however, to insist that when once a diagnosis of brain abscess has been arrived at no avoidable delay should be countenanced, for it has twice been my misfortune to see cases, definitely diagnosed as abscess, die in the night which was allowed to intervene between the diagnosis and the operation. And perhaps in cases 4, 7, 8 and 9, which ended fatally, the unsatisfactory result might have been avoided had operation been more promptly undertaken.

Dealing again for a moment solely with abscesses originating from disease of the tympanum, I would condense my experience in operative treatment into one phrase. Follow the disease, which is necessarily a logical practice founded upon the pathological facts which I have so strongly insisted upon above. In these ear cases the obviously correct line of operation is to lay open the antrum and tympanum by means of the usual radical mastoid operation, and then to follow the disease in the bone down to the affected dura. This procedure will in more than 90 per cent. of brain abscesses lead to the seat of the abscess directly and accurately. The alternative method of trephining over the temporo-sphenoidal or cerebellar lobes, with the hope of hitting off the abscess without any accurate guide as to its position, is, to my mind, obsolete and incomprehensibly illogical. When pachymeningitis externa is present, unless it is unusually extensive, it is necessary to remove with bone forceps an additional circumference of bone around the infected area, so that thorough exploration of the subjacent brain may be an easy matter.

We must next consider how the brain can be satisfactorily explored, and to my thinking the usual method of attempting to localise the abscess by means of an exploring needle is frequently unsatisfactory. In at least three of my ten cases a needle was several times introduced, and, without doubt, passed directly through the abscess cavity, and yet no pus was withdrawn. It is far better practice to make a free.

incision through the dura within the limits of the inflamed area, and then to pass the scalpel through the subjacent layer of brain substance in the direction in which the abscess is expected. This method has in my hands not yet failed to open the abscess whenever one has been present, and in a few cases in which the brain has been similarly explored on the supposition of abscess, which subsequent events proved not to be present, it has been followed by no evil results; for though, by some, free incision of the dura mater is supposed to predispose to the formation of a hernia cerebri, I have not found, nor do 1 believe, that hernia is likely to result from free incision of the dura, being rather due, as is now generally believed, to cerebritis, usually resulting from inefficient drainage of a brain abscess (*vide* case 6). If the scalpel has been introduced into the abscess, as shown by the free evacuation of pus along the blade, the orifice is easily enlarged with a pair of dressing forceps or with the finger. Should, however, free incision of the brain substance fail to localise the abscess, the forefinger must be introduced through the incision in the dura, when by palpation the abscess can usually be localised, owing to the different sensation of consistency which it gives as compared with the surrounding healthy brain substance.

Satisfactory drainage of brain abscesses is always a matter of some difficulty, and in order to eliminate as far as possible the necessity for this, it is often good practice, especially when the abscess is large, to excise the abscess floor formed by the dura and adherent cortex, when the opposite wall of the abscess will be in a short time pushed to the surface by the force of the cerebral pulsations. The cavity is then drained with a rubber tube or with gauze packing brought out through the postauricular wound, which is left unsutured.

Prognosis.—In the 1901 edition of his monograph (*supra cit.*) Körner collected 267 published cases of brain abscess, of which 212 were cerebral, with a mortality of 49·5 per cent., and 55 cerebellar abscesses with a mortality of 47·2 per cent. In the appendix of his most recent edition, Körner points out that deductions as to mortality from published cases only are likely

to be incorrect, as operators are naturally inclined to put on record cases which ended favourably, and after drawing attention to the value which would attach to the complete statistics of any clinic, or to the publication of a consecutive series of cases, gives a recent series of thirty cases which had come under his own or Schmiegelow's care ; these show a mortality of 73·3 per cent., being twenty-two out of the total of thirty, but in fourteen of these, owing usually to some complication, such as sinus thrombosis or meningitis, brain abscess was not suspected, and was therefore not looked for. Of the sixteen cases in which an abscess was found and evacuated, eight died from either encephalitis or other fatal complication existing before the operation. My own series of ten consecutive cases gives a mortality of 50 per cent., but either this or Körner's recent series is too small for any accurate deductions to be drawn from it.

In an appreciable percentage of cases (8·7 Körner) there is more than one abscess, so that though one cavity has been drained the patient does not improve and will die unless the possibility of another abscess is borne in mind. It is possible that I had two abscesses to deal with in case 5, but in many cases (as in case 6) defective drainage of a residual abscess is the correct explanation of an autopsy which may be supposed to be due to a second undrained cavity.

In analysing the series of published cases, Körner shows that a comparison between those treated by trephining and those treated, as in my series, by tracing the disease from the middle ear to its brain focus, leads us to the conclusion that the latter method gives about 8 per cent. smaller mortality ; this is interesting, and, if true, is a fact of no small importance, but though the series contained an almost equal number of cases treated by either method, it was too small and contained too many sources of possible fallacy for accurate deduction.

SIXTY-EIGHT CASES OF PERNICIOUS ANÆMIA.

By

HERBERT FRENCH, M.D., F.R.C.P.

THE cases of pernicious anæmia that were in Guy's Hospital previous to 1890 have already been recorded in these Reports by Dr. Addison, Dr. Pye-Smith, Dr. Frederick Taylor, and Dr. Hale White. The present article is a continuation of these records, embodying notes of the sixty-eight cases of the disease that were in the hospital between January, 1891, and December, 1908. The use of the term " pernicious anæmia " is purposely restricted to include no case that has not at one time or another exhibited oligocythæmia with a high colour index and no leucocytosis during life; or, if death occurred, a definite Prussian blue reaction in the liver.

THE PRUSSIAN BLUE REACTION.
(Perl's Test.)

The method of testing for the Prussian blue reaction is as follows : If a thin slice of the liver be immersed for five minutes in a 5 per cent. solution of potassium ferrocyanide, and then transferred to a 1 per cent. solution of hydrochloric acid, a Prussian blue colour begins to appear in about two minutes and goes on deepening for half an hour or more. The reaction, also spoken of as Perl's test, depends not only upon the presence of an excess of iron, but also upon that iron being in a sufficiently simple combination to respond to this ordinary chemical test.

If there is any doubt about the reaction at all, it is almost certainly not positive. Many conditions produce livers with

indeterminate greenish or greenish-blue reactions, but so far as is
known at present, pernicious anæmia alone causes it to give the
characteristic deep Prussian blue reaction of inorganic iron.

It is not the liver alone that gives this test ; the spleen and the
kidneys often do so to an almost equal extent.   Moreover, it is
possible for the Prussian blue reaction to be extremely definite
in the kidneys when the liver reaction by itself might be
indeterminate.   A case that was recently under Dr. Hale White
showed the importance of this fact very clearly, for the kidney
reacted so markedly to the Prussian blue test that there was no
doubt as to the diagnosis of pernicious anæmia, although the liver
in that particular case went but a greenish-blue colour instead of
a deep Prussian blue.

The main features of the disease are so well known that there
is no need to refer to them all in detail.   In addition to the notes
of the 68 cases themselves (pages 121 to 209), a summary of the
various points presented by them will be found at the end of the
paper, on pages 210 to 223.   The particular features to which
special attention may be directed here are the following nine :—

   i. The temperature charts of pernicious anæmia cases.

   ii. Pigmentation of the buccal mucosa in pernicious anæmia.

  iii. The size of the spleen in pernicious anæmia.

  iv. The nerve symptoms in pernicious anæmia.

   v. The gastro-intestinal symptoms in pernicious anæmia.

  vi. The state of the mouth in pernicious anæmia.

 vii. The variability of the colour index in pernicious anæmia.

viii. The injustice of the epithet " pernicious " in some of the cases.

  ix. The great difficulty there is in accurately dating the
beginning of the illness, with some thoughts that this
difficulty suggests.

I.—The Temperature Charts of Pernicious Anæmia Cases.

(Oral temperature.)

It is remarkable how constantly there is slight evening pyrexia
in pernicious anæmia.   This has often enough been noted before,
and yet it is apt to escape the attention of medical students.   As
many of the charts as were available in the 68 cases under

discussion have here been reproduced, and three points about them stand out saliently, viz.: first, that when the patient is ill enough to be admitted to hospital it very seldom happens that there is not a rise to something between 99° and 100°F. every evening; secondly, that pyrexia exceeding 101°F. is possible in pernicious anæmia, though unusual unless there is some inter-current malady such as tonsillitis or pneumonia; and, thirdly, that there is little tendency to subnormal temperatures in the morning, especially if the records are made only at 10 a.m. and 6 p.m.

Judging from what happens in other asthenic conditions, such as those associated with chronic heart disease, for example, one would not have been surprised if the temperature in a severe case of pernicious anæmia had shown a tendency to be persistently subnormal; judging from what happens in cases of chronic sepsis, on the other hand, one might have expected a moderate degree of evening rise, but at the same time a considerable drop below normal in the morning. Neither of these types of temperature chart is at all like that of most cases of pernicious anæmia, however; in this disease it may be roughly said that the more the general condition of the patient improves under treatment the less does the tendency to evening pyrexia become; but that when the patient is decidedly anæmic and ill the condition is not like that of the great majority of pernicious anæmia cases unless the patient's temperature tends to rise to something between 99° and 100·5° F. every evening without any great fall below normal at 10 a.m. in the morning. Chart after chart taken from successive cases of pernicious anæmia shows this slight but persistent pyrexia. The smallness of the variation in temperature at different times of the day in some cases is well exemplified by four-hour charts, which exigencies of space have made it necessary to publish here in the reduced morning and evening form.

II.—PIGMENTATION OF THE BUCCAL MUCOSA IN PERNICIOUS ANÆMIA.

In the next place I should like to recall to memory the remarks made by Dr. Hale White before the first meeting of the

Association of Physicians of Great Britain and Ireland, upon a case of pernicious anæmia in which there were abnormal pigmentary deposits not only in the skin, but in the buccal mucosa. It is well known that Addison's disease and pernicious anæmia may present such similar symptoms that it is sometimes difficult to be sure which malady the patient is suffering from. It was formerly a generally accepted opinion that the presence of pigmentary deposits beneath the buccal mucosa inside the lips or cheeks would be decisive in favour of Addison's disease in such a case. Unfortunately this can no longer be maintained, for in at least two cases (No. 43, p. 173, and No. 53, p. 188) in which the diagnosis was confirmed by post-mortem examination, at which the suprarenal glands were normal, there was well-marked pigmentation of the buccal mucosa. Case 43 was the one in which Dr. Hale White himself observed the phenomenon ; case 53 was mentioned by me in a paper before the Medical Society of London in 1909.

It may well be asked what rôle arsenic plays in the occurrence of this intrabuccal pigmentation in pernicious anæmia?

It is difficult to answer this question absolutely, but it seems that in the Manchester epidemic of arsenical poisoning such pigmentation within the mouth was not observed. Moreover, it is known that pathological pigmentation of the skin may occur in pernicious anæmia even when no arsenic has been given, so that seems to be no reason why it should not sometimes do so in the mouth also. Nevertheless, arsenic had been employed in the treatment of both the above cases, and therefore, although one can say that pigmentation of the buccal mucosa can occur in pernicious anæmia cases treated by arsenic, it is not possible to say absolutely that similar pigmentation can occur in pernicious anæmia cases in which no arsenic has been used.*

It may, perhaps, be added that the appearance of the buccal pigment is precisely similar to that seen in Addison's disease.

* Dr. H. D. Rolleston has recently shown a case of pernicious anæmia with buccal pigmentation previous to arsenical treatment, before the Royal Society of Medicine.

III.—THE SIZE OF THE SPLEEN IN PERNICIOUS ANÆMIA.

Passing next to a consideration of the size of the spleen in pernicious anæmia, it seems worth recording that although the general statement that the spleen is not enlarged as a rule may be true, nevertheless there are quite a number of cases in which the spleen is large enough to be readily palpated without any special expertness on the part of the observer. Clinically, out of sixty-eight consecutive cases there were twenty-four in which the spleen was felt with ease. The degree of enlargement may be compared with that which occurs in typhoid fever ; in the greater number the spleen came below the costal margin for something between half an inch and two inches ; in a few, however, the enlargement was greater, the spleen reaching down to below the level of the umbilicus in at least one.

The clinical observation of splenic enlargement in so considerable a proportion of pernicious anæmia cases is quite borne out by the results of post-mortem examinations ; big spleens are often found after death, even when they were not felt during life.

The actual weights of the spleens are known for eighteen out of the total sixty-eight cases, and they vary from 3½ ounces, or 105 grams, on the one hand, to 19 ounces, or 608 grams, on the other. Fourteen out of the eighteen weighed more than normal, and it is noteworthy that six out of them weighed no less than 10 ounces or more. The existence of a spleen that can be readily palpated is, therefore, by no means unlikely in pernicious anæmia, especially in the later stages of the disease. Too little stress is laid upon this point as a rule.

The fact that pernicious anæmia may be a cause for definite enlargement of the spleen clearly increases the number of other conditions with which, under certain circumstances, it might become confused.

*Weight of the Spleen in Eighteen Consecutive Fatal Cases
of Pernicious Anæmia.*

(Normal weight 5 ounces, or 150 grams.)

CASE.	OUNCES.	GRAMS.
35	3⅓	105
4	4	128
30	4	130
66	4½	146
33	5⅔	181
26	6½	207
39	7	221
13	7	224
32	8	246 (in a girl of 10)
51	8	248
22	9	288
48	9½	306
10	10	320
25	10⅔	341
58	13	417
17	14	448
63	15⅔	500
11	19	608

IV.—The Nerve Symptoms in Pernicious Anæmia.

Nervous symptoms may not only be prominent in cases already known to be pernicious anæmia, but they may also antedate the recognition of the blood disease by weeks or months or even years. It is not altogether infrequent for a patient to attend at a hospital for symptoms which are regarded as those of ordinary locomotor ataxy, or of lateral sclerosis, for quite a long time before the cord changes are finally recognised as being associated with pernicious anæmia.

It is not uncommon to find various degenerations in the cord post-mortem, and when these are considerable the patient may have presented symptoms suggestive of spastic paraplegia, ataxic paraplegia, locomotor ataxia, or simple ataxia, according to which parts of the cord were most affected. Peripheral neuritis may also occur, but it is difficult to say to what extent this may be due to the arsenic that is employed in the treatment of the disease.

It is less common, perhaps, for the complete signs and symptoms of any of the named diseases of the spinal cord to present themselves than for irregular nerve symptoms to appear, many of which are subjective, and, therefore, apt to be regarded as purely functional. In case 1, for instance, severe pains in the back, diagnosed as lumbago for lack of a better name, had been a prominent symptom for years before the pernicious anæmia was recognised. In different cases the nerve signs and symptoms, exclusive of headaches, gastric pains, giddiness, or buzzing in the ears, which are doubtless due to the anæmia directly, were as follows :—

Case 1. Lumbago and paresis of the legs. Many acute attacks of pain in the back. Reflexes natural.

Case 4. Delirium with violence. Optic atrophy. Dr. Savage said symptoms were those of general paralysis of the insane.

Case 5. Giddiness and a sense of something pumping inside his head.

Case 7. Severe neuralgia. Pains in the back, in the limbs, and in the right flank.

Case 8. Supra-orbital herpes.

Case 9 Extensive peripheral neuritis, very probably alcoholic. Reaction of degeneration in all the muscles of the legs.

Case 10. Knee-jerks absent; other reflexes natural. Drowsiness and Cheyne-Stokes respiration towards the end for some days.

Case 11. Pains in the chest and abdomen; giddiness. Severe itching of skin.

Case 14. Troublesome tingling of fingers and toes; acroparæsthesia, but nerve reflexes natural.

Case 15. Knee-jerks absent.

Case 16. Tearing pains in his chest and abdomen, and feelings as though his body were being tightly gripped and squeezed. Reflexes natural.

Case 17. No clinical signs, but degeneration of posterior columns post-mortem.

Case 18. Thoracic pain. Anæsthesia of feet. "Could not feel sure of his foothold owing to numbness in his soles, so that he used to stumble like a drunken man sometimes." Knee-jerks natural.

Case 20. Numbness of hands and feet. Buzzing noises in ears.

Case 22. Knee-jerks decidedly exaggerated.

Case 23. Loss of power in the legs. Very definite lateral sclerosis, first symptoms in case. Incontinence of urine. Knee-jerks exaggerated. Ankle clonus both sides. Also undue tingling of hands and arms.

Case 25. Described as "neurotic and hysterical." Left knee-jerk just obtainable, right not obtained. Decided anæsthesia of all the finger tips.

Case 26. Nervous system at first natural; but retention of urine before death.

Case 27. Decided numbness of the fingers. Reflexes natural.

Case 28. Concentrically contracted fields of vision. Optic neuritis. Knee-jerks difficult to obtain. Wasting. Shooting pains in arms and legs.

Case 29. First treated for hypochondriasis. Numbness and tingling in finger tips. Knee-jerks absent, or very difficult to elicit. Pupils natural. Once hands and arms tossed about continually and everywhere. Expectoration in all directions, and fits of imbecile laughter.

Case 30. Reflexes all natural. Much troubled by knocking noises in head and by giddiness on stooping. Everything she ate tasted sweet, even acid and salt things did.

Case 32. Pains in limbs, especially calves of legs.

Case 33. A tight feeling across the chest.

Case 34. Both knee-jerks very brisk. Ankle clonus in one foot, not in the other.

Case 36. Decided lateral sclerosis; prominent enough to be the early diagnosis. Knee-jerks both exaggerated. Ankle clonus, and Babinski's sign, both sides. Increased sensibility to heat and cold in patches of legs. No anæsthesia. Definite spasticity of legs.

Case 38. Weakness of arms and legs; loss of control over defæcation.

Case 42. Painful abdominal symptoms leading to diagnosis of " enteroptosis."

Case 43. Anæsthesia to electrical stimulation of the legs; not to cutaneous sensibility. Both plantar reflexes extensor.

Case 44. Greatly troubled by numbness of both hands and both feet.

Case 46. Reflexes natural; but great numbness of fingers and toes; inability to put hand into cold water without fingers going dead, even in summer.

Case 47. Marked numbness in hands and feet; attacks of sweating, giddiness, and blurred vision when at work, so that he had to clutch something to avoid falling. Knee-jerks unduly brisk, but plantar reflex flexor, and no clonus.

Case 48. Latterly had become extremely nervous and irritable. Light-headed. Delusion as to bowl of flowers on table. Reflexes natural.

Case 49. Four years ago her fingers began to tingle, this tingling soon spread to whole of body and legs. A year later, left leg became very weak and shaky, and some little time later her right leg followed suit. Noises in head very troublesome. Wrist, elbow, and knee-jerks all increased. Extensor plantar reflex on both sides. Ankle clonus and spasticity.

Case 52. Right plantar reflex persistently extensor; though left was flexor. No ankle clonus.

Case 53. Ringing in ears. Curious subjective sensation of paræsthesia, in particular, her thighs felt " too hot inside and too cold out," in a way which struck her as abnormal and inconvenient. Knee-jerks absent.

Case 54. Sent to Insane Asylum on account of mania with delusions, impulsive and dangerous. Reflexes natural.

Case 55. Curious feelings in legs from knees downwards, " as if walking in deep snow." Reflexes natural.

Case 56. Started with pains in back and chest, spreading to buttocks and legs, and getting worse for three years. Reflexes natural. Suffered from a good many symptoms that were regarded as " neurotic."

Case 60. Throbbing in head; pains in head; sleeplessness requiring sleeping draughts.

Case 62. Reflexes natural, but patient complained of " weakness in every joint, and of a ' deadness' in the region of the joints."

Case 65. Eyesight began to fail, without objective lesion; thought possibly tobacco amblyopia. Hands and feet " seemed to be numbed." Reflexes natural.

Case 67. Pains in abdomen, head, and arms. Ordinary reflexes natural.

Case 68. Much bothered by black spots in front of eyes, severe headaches, and great thirst. Knee-jerks very brisk, but otherwise reflexes natural.

These are the various nerve signs and symptoms presented by forty-four cases out of sixty-eight. The remainder did not spontaneously complain of anything similar, and nothing particular about the nervous systems attracted the attention of the ward clerks who wrote the reports. If forty-four out of sixty-eight cases present nerve symptoms, however, of degrees varying from subjective numbness of fingers and toes to definite spastic paraplegia, it is clear that there is at least a possibility of a case of pernicious anæmia now and then being treated solely for nerve trouble unless some stress is laid upon the well-known possibility of pernicious anæmia being associated with pathological changes in the spinal cord and peripheral nerves.

V.—GASTRO-INTESTINAL SYMPTOMS IN PERNICIOUS ANÆMIA.

In view of Dr. William Hunter's opinion that pernicious anæmia is a specific disease due to a hæmolysing poison or toxin derived from the alimentary canal, the prevalence or otherwise of gastro-intestinal symptoms in the earlier stages of the malady becomes one of considerable interest. Dr. Hale White, in his paper on pernicious anæmia in Vol. XLVII. of these Reports

(1890), laid particular stress upon this, and after careful consideration of each case states, "We may therefore conclude that dyspeptic symptoms, particularly vomiting and diarrhœa, are very common in genuine pernicious anæmia, being present in almost half the cases, that they are often very severe, and that constipation is one of the least common of the dyspeptic symptoms." This conclusion is more than borne out by the present cases, although there is a definite number of them in which gastro-intestinal symptoms are entirely absent. In nine of the total sixty-eight they are not mentioned (cases 4, 12, 20, 42, 43, 51, 54, 64 and 68) ; in fourteen others they are definitely mentioned as not present (cases 3, 6, 9, 10, 15, 16, 18, 25, 26, 31, 56, 57, 67 and 68), although in six of these diarrhœa or vomiting developed after arsenical treatment had been adopted (cases 3, 10, 18, 56, 67 and 68); whilst in the remaining forty-five there were definite gastro-intestinal symptoms comparatively early, and presumably before arsenical treatment was begun. It needs to be borne in mind, of course, that many maladies cause "indigestion," and also that diarrhœa is more significant than vomiting, seeing that the latter may be due directly to the anæmic state, especially when an anæmic person tries to exert himself beyond his physical powers—so-called "anæmic vomiting." Nevertheless the following summary of the gastro-intestinal symptoms, in forty-five out of sixty-eight consecutive cases, strongly suggests that they are connected in a direct and important way with the pathology of the disease :—

Case 1. Diarrhœa and loss of appetite.
Case 2. Bilious attacks and vomiting of bile. Severe diarrhœa.
Case 5. Bilious attacks and vomiting on and off for years ; severe bouts of diarrhœa.
Case 7. A marked case of vomiting. Also " for twenty-five years every little thing has seemed to cause diarrhœa."
Case 8. Bilious attacks. Severe diarrhœa, on one occasion suggesting cholera.
Case 11. Severe diarrhœa each year. At other times fæces are small hard globular masses like iron rust.
Case 13. Diarrhœa, severe enough to be diagnosed as cholera.
Case 14. Diarrhœa for a long while past, up to as many as fifty motions a week.
Case 17. " English cholera." Severe vomiting. Has to be very careful of diet or suffers severe abdominal attacks and diarrhœa.

Case 19. " Indigestion " for years.
Case 21. Vomiting, especially in the morning.
Case 22. Very troublesome nausea and vomiting.
Case 23. Diarrhœa and vomiting.
Case 24. Persistent and severe diarrhœa for three and a half years.
Case 27. A decided tendency to diarrhœa. " Indigestion very readily produced."
Case 28. Vomiting.
Case 29. Constipation and vomiting.
Case 30. " Indigestion " for years.
Case 32. Vomiting bouts.
Case 33. Diarrhœa. Ulcerative colitis (q. v.).
Case 34. Dyspepsia; alternate bulimia and anorexia; vomiting.
Case 35. Constipation so severe that plumbism was diagnosed owing to occupation as painter.
Case 36. Severe diarrhœa.
Case 37. Vomiting.
Case 38. Vomiting and diarrhœa.
Case 39. Vomiting. Chronic colitis (q. v.).
Case 40. Severe " bilious attacks."
Case 41. Severe bouts of diarrhœa, the first of which was so severe that typhoid fever was diagnosed.
Case 44. Vomiting after food. Constipation.
Case 45. Vomiting on the least thing. Severe diarrhœa.
Case 46. Vomiting, diarrhœa, and " indigestion " on and off for four years. One attack taken for " enteric fever " at Naples.
Case 47. Vomiting bout, quite sudden in onset.
Case 48. Diarrhœa on and off for a year.
Case 49. Severe diarrhœa.
Case 50. Constipation very troublesome.
Case 52. Vomiting and severe diarrhœa for which the patient was warded in Guy's a year before pernicious anæmia was recognised.
Case 53. Loss of appetite and " dyspepsia."
Case 55. " Bilious vomiting " without diarrhœa.
Case 58. No diarrhœa; vomiting so severe that nothing but plain water could be kept down. Admitted to the surgical side with a view to gastro-jejunostomy for ulcer. No gastric lesion present at post-mortem examination.
Case 59. " Dyspepsia " for five years. Severe diarrhœa and vomiting for four months.
Case 60. Dyspepsia for two years; all the teeth removed with a view to curing this. Vomiting on and off for ten weeks.
Case 61. Vomiting after food.
Case 62. " Dyspepsia " for eleven years. Teeth removed on this account. Recent diarrhœa, but arsenical treatment well borne, up to eleven minims of the liquor thrice daily.
Case 63. " Gastric ulcer symptoms precisely like those of an attack years before." Vomiting, even of fluids. Hæmatemesis.
Case 66. " Indigestion " for ten years; many teeth extracted on account of this.

Gastric HCl.

There is a note as to the gastric HCl. in three cases (Nos. 51, 57 and 68). In the first free HCl. was abundant, in the second " deficient," in the third " absent."

VI.—THE MOUTH IN PERNICIOUS ANÆMIA.

The prevalent view as to the relationship between a septic state of the tooth sockets, gums or mouth and pernicious anæmia is that this sepsis causes, not " pernicious " but " septic " anæmia, the latter having a low colour index even if it reaches a severe degree. Some hold, however, that this " septic " anæmia is one of the conditions which particularly predisposes the patient to suffer from the effects of that unknown gastric or intestinal toxin which is supposed to be the specific cause of pernicious anæmia itself. In short, oral sepsis causes "septic anæmia," and "septic anæmia" predisposes to pernicious anæmia. The commonness of carious and dirty teeth amongst pernicious anæmia cases in hospital cannot be gainsaid, but then nearly every hospital case, whatever the disease for which he is admitted, has faulty teeth. If the latter were a potent cause of pernicious anæmia it should be a common malady. So often, however, are the teeth referred to in text-books as being particularly septic and carious in this disease that special stress may perhaps be laid upon the fact that the existence of a well-cleansed set of natural teeth in good repair by no means rules out the diagnosis of pernicious anæmia. Thus in case 9 there was a special note that " the teeth are in excellent condition." In case 10 " the teeth were in excellent condition, and only two were missing." In case 14, " The teeth are good and the mouth is clean and sweet." Case 15, " Mouth clean. Teeth noted as being exceptionally good." Case 21, " The teeth were all good." Case 37, " Mouth clean and teeth in particularly good order." Case 41, " Teeth and mouth in remarkably good order." Case 44, " A good clean mouth and clean teeth." Cases 16 and 29 were entirely edentulous from age—61 and 67 years respectively—and case 59 was, curiously enough, a dentist.

Lest the cases above should convey the erroneous impression that the teeth are apt to be particularly good, it is only right to give the following notes from the remaining cases in which their condition is mentioned :—

Case 5. Tongue and mouth clean, but pallid.

Case 7. Tongue clean, but teeth in a bad state.

Case 17. Tongue sore and throat parched.

Case 18. Teeth in very fair order.

Case 23. Mouth clean, but teeth in only fair condition.

Case 25. Teeth in a very bad state.

Case 27. Teeth good, but black from smoking.

Case 30. Teeth scanty, but those left are clean ; no stomatitis.

Case 31. Teeth carious and in poor condition ; mouth so sore that the patient could not smoke at all during five weeks previous to admission.

Case 34. Teeth much decayed.

Case 35. Breath foul ; furred, flabby tongue ; carious teeth.

Case 36. Teeth decayed and very septic.

Case 39. Teeth in a bad state, but only so since taking medicine, according to the patient.

Case 45. Started with very septic sore throat.

Case 46. Considerable pyorrhœa alveolaris.

Case 47. Teeth few ; but those left were clean and healthy.

Case 48. Mouth dirty and teeth bad.

Case 49. No teeth of her own, but a good set of false ones.

Case 50. Teeth carious, but mouth clean, as the patient had long been in the habit of using potassium permanganate as a mouth wash.

Case 51. Teeth had been very carious, but they had been replaced by dentures.

Case 53. Purulent tooth sockets.

Case 54. Teeth carious.

Case 55. Teeth bad and tongue coated.

Case 56. Teeth very septic and outstanding from gums, and tongue coated white.

Case 57. Teeth not very bad, but not clean, and several carious.

Case 59. A dentist. The teeth had been good until four months before admission, but now they were not so good, and there were sore ulcers inside the cheeks where the latter impinged against the bad teeth.

Case 60. Teeth all removed two years before for dyspepsia.

Case 61. Had been having trouble with teeth for two years. Alveolar abscess at one time. Stumps left were very septic.

Case 63. Mouth clean, but teeth much decayed.

Case 65. Clean mouth, but many teeth carious.

Case 66. Six years before admission had been supplied with false teeth for the cure of long-standing dyspepsia. Now came in to a surgical ward for necrosis and gangrene of the jaw after tooth extraction. Died in a week.

Case 67. Teeth carious and much pyorrhœa alveolaris, though rest of
          mouth clean.

Case 68. Several decayed teeth had to be removed, but mouth in general
          clean ; much thirst.

VII.—The Variability in the Colour Index in Pernicious
Anæmia.

The final clinical criterion of pernicious anæmia at present is
the occurrence of a high colour index with oligocythœmia, and
without leucocytosis.   It is very important to realize, however,
that the fact that the colour index proves to be low, or at least
not high, when the blood is examined once only, or even more
than once, is no proof that the condition is not one of pernicious
anæmia ; for when a series of blood counts are made at intervals
in the same case with the best instruments at our disposal, it is
comparatively common to find that there are periods when the
colour index is less than one, as well as other periods when it
is greater than one.   Roughly speaking, the index tends to be
highest when the patient is most ill and anæmic, and to become
lower as the condition improves.   This is no absolute rule,
however, for a high colour index may persist even when much
improvement has occurred, and, on the other hand, a low index
is sometimes found when the patient is very ill.

It is astonishing how quickly the index may vary ; even when
the instrumental error is reduced to a minimum in the hands of
skilled observers there may be a high colour index one week and
a low one the next ; such radical changes in the character of the
blood have been attributed to derangements known as " blood
storms."

The blood counts will be found appended to the abstract of the
report of each patient at the end of this article, and many of them
serve to demonstrate the fact that a pernicious anæmic blood may
have a low colour index at times.   I may add, perhaps, that the
diagnosis was in more than one such case confirmed by autopsy,
so that there can be no doubt as to correctness upon that score.
To pick a case almost at random, No. 45 shows variations in the
colour index from as low as 0·791 to as high as 1·750, and out of

the five counts made at intervals, two were greater and three were less than one. Case after case shows the same kind of thing (see page 221). I think the point is one of great importance. It unfortunately adds to the difficulty of diagnosis, but it teaches that pernicious anæmia is not by any means to be excluded by a single blood count.

VIII.—THE INJUSTICE OF THE EPITHET "PERNICIOUS" IN SOME OF THE CASES.

An entirely different matter now presents itself for discussion, and that is, the injustice of the epithet "pernicious" in some of the cases.

Pernicious, in its lay sense, is a very strong term, and its use leads the medical student to gather an erroneous idea of the prognosis in pernicious anæmia. It is true that hardly any patients in whom typical pernicious anæmia has developed ever become completely well again. It is also true that the fatal ending of the disease sometimes comes within a month or a few months of what seems to be the beginning of the disease. On the other hand, the average duration of pernicious anæmia, from the time of its recognition until the patient dies, is in a fair number of cases to be measured in years rather than in weeks or months, besides which the illness is not one of continuous downward progress like that of carcinoma of the stomach, for example, for nothing in medicine perhaps is so striking as the way in which, even if the rally be only temporary, a patient who may seem to be *in extremis* from pernicious anæmia, with his red corpuscles under 20 per cent. of normal, may recuperate, not only once, but sometimes several times. If one were condemned to suffer from a fatal malady, but were given the choice between malignant disease of the upper part of the alimentary canal, for example, on the one hand, or from pernicious anæmia on the other, it is clear that in either case one might be dead within the year, but that if one chose pernicious anæmia one would have a better chance than with gastric carcinoma of living for several years.

The intervals between the recognition of the pernicious anæmia by blood count and the time of death in the fifty-one cases in which, out of the total sixty-eight, the ultimate fate of the patient is known, were as follows:—

One year or less, thirty cases:—
    Less than one month, eight cases (Nos. 22, 26, 32, 40, 58, 61, 63, 66).
    One to three months, eight cases (Nos. 4, 9, 17, 24, 29, 37, 51, 60).
    Three to six months, five cases (Nos. 10, 25, 33, 46, 56).
    Six to twelve months, nine cases (Nos. 12, 13, 14, 23, 27, 35, 39, 49, 65).
One to two years, thirteen cases:—
    Twelve to eighteen months, nine cases (Nos. 3, 20, 28, 42, 44, 48, 52, 53, 55).
    Eighteen to twenty-four months, four cases (Nos. 8, 18, 30, 41).
Two to nine years, eight cases:—
    Two to three years, four cases (Nos. 11, 34, 43, 57).
    Three to four years, two cases (Nos. 36, 47).
    Up to nine years, two cases (Nos. 1, 7).

It is important to remember that the above figures apply to the time that elapsed between *recognition* of the disease and its termination; the duration from the earliest symptoms is often much longer, as will be discussed immediately.

It will be seen that thirty cases died within the year, but that twenty-one survived for one year or more, eight out of fifty-one cases living for something between two and nine years after the time when pernicious anæmia had been diagnosed beyond doubt. The word "pernicious" is rather too strong to be applied to a condition in which the prognosis, though bad, is no worse than this. Lymphatic leuchæmia is far more pernicious a complaint than is pernicious anæmia. I should like to see the older term, "Addison's anæmia," used instead.

It will be said that I have picked out a particularly favourable case when I refer the reader to the notes about Charles R. (Case No. 1, page 121). The allegation is true, but his story illustrates so well both the power some of these patients have of rallying, and also the length of time they may survive, and, further, the fact that their initial symptoms—lumbago in this case—may not seem to have any relation to a blood disease, that I venture to draw special attention to it.

IX.—THE DIFFICULTY FREQUENTLY MET WITH IN ACCURATELY
DATING THE BEGINNING OF THE ILLNESS, WITH SOME
THOUGHTS THAT THIS DIFFICULTY SUGGESTS.

I have just referred to the length of time that elapses in
different cases between the recognition of the pernicious anæmia
and the death of the patient. The recognition of the disease is
chiefly by means of blood counts; but I should like to lay great
stress upon the fact that in the majority of cases the blood count
recognition by no means coincides even with an early stage of
the disease, much less with its actual beginning. When one
reads through the impartial histories of these cases as recorded
by medical ward clerks, one is struck again and again by the fact
that symptoms have been present for months, years, or even
many years, before the anæmia itself becomes pronounced. I quite
grant that there are a few cases which seem to be acute (*e.g.,*
Nos. 6 and 50); in most cases, however, the onset is quite insidious,
and in quite a number the earlier symptoms are attributed to
some entirely different malady, typhoid fever, for example (case
46), or English cholera when diarrhœa was a prominent symptom
(cases 13 and 17); a chronic nerve disease (case 36); functional or
organic disorder of the stomach (case 63); and so on.

The sixty-eight consecutive cases themselves dated their illness
back for at least the following lengths of time prior to its
recognition :—

For less than one month in three cases (Nos. 6, 47, 50).
Between one and three months in seven cases (Nos. 9, 10, 26, 30, 48, 51, 61).
Between three and six months in three cases (Nos. 18, 35, 45).
Between six and nine months in eight cases (Nos. 20, 31, 34, 37, 53, 55,
    57, 63).
Between nine and twelve months in four cases (Nos. 22, 33, 54, 58).
Between one and two years in eight cases (Nos. 23, 25, 27, 28, 44, 52, 65, 67).
Between two and three years in seven cases (Nos. 2, 3, 4, 38, 41, 42, 60).
Between three and four years in four cases (Nos. 16, 24, 29, 56).
Between four and five years in seven cases (Nos. 7, 8, 12, 21, 32, 46, 49).
Between five and six years in two cases (Nos. 11, 59).
Between six and seven years in two cases (Nos. 13, 15).
Between seven and eight years in three cases (Nos. 17, 36, 39).
Between eight and nine years in two cases (Nos. 40, 64).
Between ten and eleven years in one case (No. 14).
Between eleven and twelve years in two cases (Nos. 62, 66).
Between fifteen and sixteen years in one case (No. 1).

In case 19 it was " some years ;" in case 43 it was " long and indefinite ;" in case 26, classed above as two months, it may really have been twenty years; in case 7, classed above as four to five years, it may really have been twenty-five years ; in case 8, classed above as four to five years, it may really have been twenty-six years ; whilst in case 5, classed above as six to seven years, it may really have been no less than forty-four years.

I should like to recall the case of Charles R. (No. 1), quoted just now, to illustrate what I mean. I see no lack of continuity in the history of his case from the original attacks of what appeared to be " lumbago" sixteen years before pernicious anæmia was diagnosed, to the patient's death from the latter disease, eigbt years after it was recognised by blood counts.

There are many other examples of similar difficulty in deciding when the pernicious anæmia really began, as will be seen if the detailed notes of the cases are consulted.

In the case of Annie P. (No. 46) for example, on inquiring into the nature of the " typhoid fever," it transpired that the symptoms were mainly diarrhœa and pyrexia, and that the patient was kept in bed for it for only four days. It seems clear, I think, that some name had to be given to an obscure febrile illness, and that typhoid fever seemed to fit it at first; but time showed, I think, a direct continuity between that illness and undoubted pernicious anæmia.

It might be urged that pernicious anæmia was not really present at the time of the " enteric " attack, but that the latter predisposed to it, and was in a way its cause. I think, however, that our clinical knowledge of the disease is more likely to be advanced if we allow that the lumbago in the case of Charles R., and the diarrhœa and pyrexia in that of Amelia P., and other symptoms in other cases, were really the earliest symptoms of a disease of which the later stages are characterised by profound anæmia, a high colour index, and a Prussian blue reaction in the liver. If this be so, then pernicious anæmia is the name for but a late phase of a more general disease, which is at present unnamed. I would suggest a comparison between it and phthisis in this respect. It is not so very many years since it

was impossible to diagnose early phthisis, and consumption was
regarded as essentially fatal because it was only recognised when
it had already passed beyond the stage when it was curable.
The end of a phthisical person may even now be very rapid by
galloping consumption, comparable to the acute cases of
pernicious anæmia ; or the end may be gradual with periods of
recovery and relapse extending over months or years, comparable
to the course of ordinary pernicious anæmia as we now under-
stand that term ; on the other hand, if recognised at a stage at
which our grandfathers would have denied the existence of
phthisis altogether, consumption may be completely cured ;
healed phthisis is found in a large proportion of post-mortem
examinations at a general hospital in patients who may never
have been suspected to have had phthisis at all. I feel sure that
pernicious anæmia as we know it is but a late stage of that which
may be much commoner than we think, recovering spontaneously,
perhaps, in many cases as phthisis does in others, breaking out
into an acute phase in others, running a subacute or chronic up-
and-down course in yet others. We are now able to recognise
phthisis early, by bacteriological and other means, in a way that
our forefathers could scarcely have believed possible. I hope
that similar early recognition of pernicious anæmia will also
become possible as time goes on. It is recognised far earlier
now than it used to be ; and perhaps if it were thought of and
diagnosed earlier still, some at least of the patients might be
cured. The two factors in diagnosis to which it would seem
that special attention should be directed are the blood on the one
hand and urobilin in the urine on the other.

Conclusion.

In conclusion, the chief points that an attempt has been made
to bring out in this paper are: first, that some evening pyrexia
is seldom absent in pernicious anæmia cases that are decidedly
ill ; secondly, that pigmentation within the mouth of precisely
similar character to that seen in Addison's disease may occur in
pernicious anæmia cases treated with arsenic ; thirdly, that the
spleen is to be felt in about one-third of the cases, and that it

is really enlarged; fourthly, that nerve symptoms are not at all uncommon in pernicious anæmia; fifthly, that gastro-intestinal symptoms, particularly vomiting, diarrhœa, and "bilious attacks," occur early in more than one-half the cases, though in others they may be entirely absent; sixthly, that although there is often oral sepsis, pernicious anæmia may develop in the presence of apparently perfect teeth; seventhly, that the colour index, though typically higher than 1 when an advanced stage of the disease has been reached, is not always nor continually high, especially during a period of improvement in the patient's condition, when it may be actually low; and lastly, that pernicious anæmia as we now know it is very possibly only a late and almost incurable stage of a disease which it is to be hoped will some day be recognisable early enough to be cured.

(For the summary of the other points presented by the cases see pages 210 to 223.)

ABSTRACTS OF THE NOTES OF THE SIXTY-EIGHT CASES.

[N.B.—When no mention is made of any particular point, it signifies that there was no mention of it in the original report. If, for instance, "urobilin" is not mentioned, it cannot be assumed to have been absent; if it had been looked for and not found it would be mentioned as "no urobilin found," and so on.]

(The References are to the Medical Ward Reports.)

CASE 1.—Ref. Nos., Vol. 109, No. 89; Vol. 114, No. 64; Vol. 123, No. 104; Vol. 147, No. 96; Vol. 153, No. 113.—Charles R., æt. 45; a brick-layer. First admitted under Dr. Pavy, in 1889, for mental irritability, weakness in the legs, and pain in the lumbar region. His colour at that time was not apparently abnormal, and the diagnosis made was *lumbago and paresis of the legs*. The pains in the back were very acute, and the patient had had three or four attacks a year for the previous fifteen years. There was no hæmaturia nor other indication that the pains might have been due to renal colic, and lumbago seemed to fit the case. In view, however, of its subsequent course it seems at least possible that the pains were similar to those which other pernicious anæmia cases often complain of in one part of the body or another. Less than a year later, in January, 1890, the patient was re-admitted, under Dr. Pavy, for loss of physical strength, failure of appetite, diarrhœa, and night sweating, and the skin was now pale and waxy, and had been obviously so for more than two months. The lungs and heart were natural. There were no retinal hæmorrhages, but occasional specks of blood were expectorated. There was no other bleeding. The urine was high coloured; it contained no albumin, blood, nor sugar. The blood count indicated pernicious anæmia. The patient was treated with pilula colocynthi et hyoscyami, and mistura ferri et ammonii citratis, and improved in general condition, though the blood count remained much the same. By September, 1891, the patient was so weak that he could not work, though he had worked between his discharge and then. He was re-admitted, under Dr. Washbourn, and was in hospital from September 4th, 1891, to November 30th, 1891. The attacks of pain in the loins were still continued, and they were very bad. There were neither enlarged glands nor spleen, no vomiting, and no diarrhœa. Treatment was now by means of liquor arsenicalis, which was increased up to mix. three times a day, with material relief to the anæmia. He went out in November, 1891, and remained well enough to work, on and off, for over four years, before repetition of his old weakness and pallor compelled him to seek hospital treatment again. He was under Dr. Hale White, in Clinical Ward, from February 7th, 1896, to March 9th, 1896. He presented the typical pale yellow colour. His tissues

were flabby, but not wasted. The urine sometimes exhibited a marked urobilin band spectroscopically, sometimes none. The temperature was typically up to 100° F. every night, and not below 98° F. in the morning as a rule. The nervous reflexes were natural. Arsenical treatment was adopted, and some relief ensued. He was discharged able to walk about, but unable to do labourer's work. He slowly relapsed, and was readmitted, under Dr. Goodhart, on March 1st, 1897. He seemed to get progressively worse, and yet he lived for two years after his discharge on May 20th, 1897. Mrs. R. writes, on August 15th, 1907 : " Mr. R. died two years after leaving Guy's Hospital, suffering from prostration and great pains in his head ; it was indeed sad to see such suffering, and the brain very much affected." During his last stay in hospital the temperature was again typically between 99° F. and 100° F. each night. The spleen, formerly not felt, now came two inches below the ribs, and the liver came one inch below the costal margin in the right nipple line. Ophthalmoscopic examination revealed neither optic neuritis nor retinal hæmorrhage. The blood counts were as follows :

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
February, 1890	2,400,000	48	53	1·104	—
March, 1890	2,400,000	48	55	1·148	—
18 Sept., 1891	1,400,000	28	28	1·000	—
25 „ „	1,100,000	22	25	1·136	—
5 October, 1891	1,800,000	36	35	0·972	—
19 „ „	2,100,000	42	35	0·833	—
26 „ „	1,800,000	36	36	1·000	—
29 „ „	1,800,000	36	40	1·111	—
31 „ „	2,000,000	40	40	1·000	—
2 Nov. „	2,900,000	58	50	0·862	—
9 „ „	3,350,000	67	60	0·895	—
7 Feb., 1896*	1,250,000	25	30	1·200	—
13 „ „	1,500,000	30	35	1·166	—
18 „ „	1,500,000	30	35	1·166	—
24 „ „	1,250,000	25	30	1·200	—
27 „ „	1,200,000	24	30	1·250	—
9 March „	1,000,000	20	25	1·250	—
19 „ „	800,000	16	25	1·562	—
8 April „	700,000	14	20	1·429	—
22 „ „	1,500,000	30	30	1·000	—
2 May „	2,150,000	43	32	0·744	—
9 „ „	2,750,000	55	38	0·691	—
11 March, 1897†	3,000,000	60	30	0·500	‡
22 „ „	1,900,000	38	25	0·659	—
5 April „	1,050,000	21	15	0·714	—
12 „ „	650,000	13	16	1·231	—
27 „ „	700,000	14	26	1·857	—

* Marked poikilocytosis.
† Many megalocytes and poikilocytosis, and some nucleated red cells.
‡ No leucocytosis.

The temperature chart was as follows :—
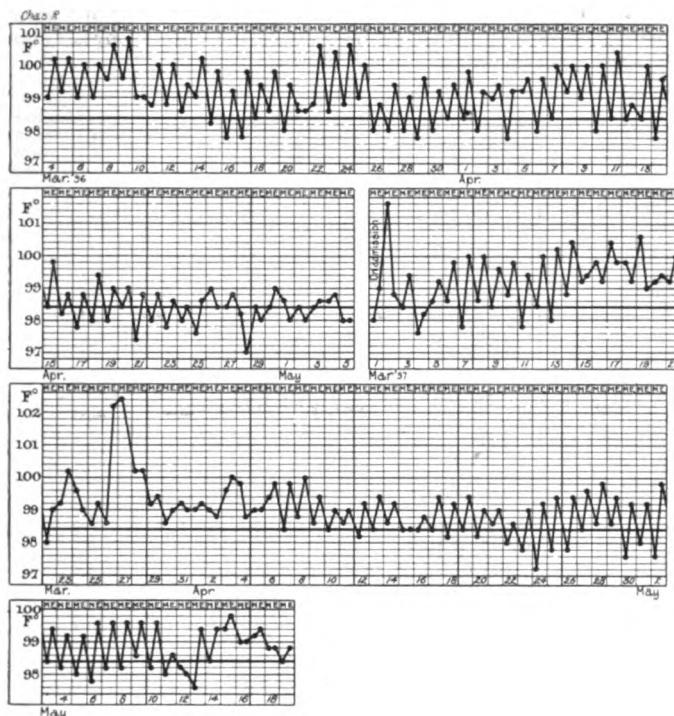
CASE 2.—Ref. No., Vol. 120, No. 49.—John H., æt. 40, a coachman by occupation, and a hard worker, was in hospital under the care of Dr. Taylor from March 17th to April 25th, 1891 ; attempts to trace him since then have failed. He began to ail two years previous to admission. Up till then he had enjoyed robust health Without apparent cause he developed a gradual inability to perform his physical work with so much energy as usual, and he had occasional attacks of vomiting, bringing up bile-stained fluid, but no blood. He also had severe diarrhœa, and after these symptoms began there was œdema of his feet. Both diarrhœa and vomiting had been present more or less all the time. The heart was of normal size, but exhibited a hæmic systolic bruit at the impulse and in the pulmonary area, and over the veins in the neck. The lungs were natural. There was a certain amount of eczema of the scrotum. The only hæmorrhages were those in the retinæ, where there were many. Neither liver nor spleen could be felt. The urine was of a pale sherry colour, and had a specific gravity of 1014 ; it contained no albumin, sugar or blood. Neither indican nor urobilin were mentioned.

The skin was of the typical primrose colour, and it had no undue pigmentation. The patient's weight was 140 lbs. When in bed he improved rapidly under arsenical treatment, though previously, while he remained up and about, he had been going down-hill under similar treatment. How long his improvement lasted is not known.

Date	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
21 March, 1891	1,600,000	32	36	1·125	—
31 „ „	1,500,000	30	32	1·066	—
16 April, „	2,300,000	46	58	1·261	—
25 „ „	3,200,000	64	70	1·094	—

Note.—Films showed an extreme degree of poikilocytosis.

The temperature chart was as follows:—
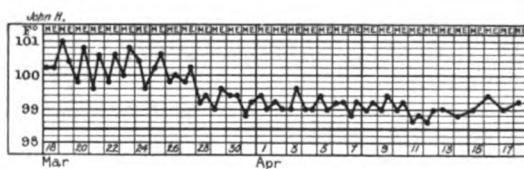
CASE 3.—Ref. Nos., Vol. 119, No. 76, and Vol. 133, No. 175.—John D., æt. 57, a farm labourer, was first admitted under Dr. Pye-Smith in 1891 for piles, weakness and swelling of his hands, feet, and scrotum, with evidence of ascites, a local systolic apical bruit, a liver that could be felt one inch below the costal margin, but no palpable spleen; the urine was free from albumin. During his stay in hospital that year the red corpuscles rose from sixteen per cent. of normal to sixty per cent. No definite diagnosis was made beyond " severe anæmia, probably due to loss of blood from hæmorrhoids." The patient remained well for two years; but seven weeks before his re-admission in 1893 he had to take to his bed again, as he was too weak to walk. He was re-admitted on April 19th, 1893, and re-discharged relieved on June 21st, 1893. He had the typical lemon-yellow colour, and was extremely weak though well covered. There was moderate œdema of the ankles, and possibly slight ascites. The temperature was usually 99° or over each night. There were no retinal nor other hæmorrhages. The urine contained neither albumin nor urobilin. Flatus and diarrhœa became so troublesome when arsenic was given that it had to be stopped; oxygen inhalations seemed to do good. He relapsed soon after his discharge, and was admitted to Hendon Infirmary under the name of John Elliott, alias John Duke; he was buried from Hendon Union on April 17th, 1894. The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Zeiss.		Gowers.		
On admission 1891	800,000	16	—	—	—
On discharge 1891	3,000,000	60	—	—	—
20 April, 1893 ...	880,000	18	30	1·666	*
26 ,, ,,	880,000	18	33	1·833	—
4 May, ,,	1,400,000	28	33	1·179	—
10 ,, ,,	1,450,000	29	35	1·207	—
18 ,, ,,	1,750,000	35	40	1·143	—
25 ,, ,,	1,750,000	35	35	1·000	—
1 June, ,,	1,100,000	22	38	1·727	—
8 ,, ,,	1,500,000	30	36	1·200	—

* There was no leucocytosis.

The temperature chart was as follows :—
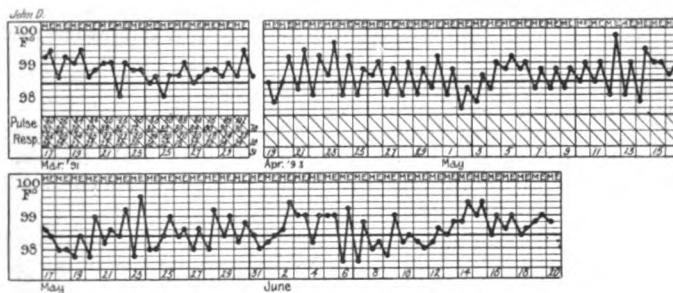
CASE 4.—Ref. No., Vol. 123, No. 105 ; Post-mortem No. 127, 1891.—
Ann W., æt. 55, a housewife, was sent up to Guy's Hospital as a case
of "jaundice." A married woman, she had been "jaundiced" thus for
two years, off and on, during which time she had been several times
incapacitated by severe attacks of diarrhœa. In the interval between these
attacks she was liable to constipation. She was admitted into Clinical,
under Dr. Perry, on March 20th, 1891, and she died on April 12th, 1891.
During the fortnight before she came in she had vomited five times, and
latterly she had become delirious and violent. Her pulse rate varied from
96 to 120, her respiration rate from 16 to 20, and her temperature was seldom
below 99° F. and seldom above 100° F., though three times it reached
101·6° F. She was not jaundiced at all. The skin was the typical colour of
pernicious anæmia. The bones were not tender. Neither liver nor
spleen could be palpated. There was no enlargement of the heart, but a
hæmic bruit and a bruit de galop. The urine had a specific gravity of 1030,
and it contained 0·7 parts per thousand of albumin, but no blood and no
sugar. There were extensive retinal hæmorrhages, together with older
choroiditis and optic atrophy, which may have been syphilitic. The patient's
mental symptoms suggested general paralysis of the insane, in which Dr.

Savage, who saw her, also agreed. The blood count and the Prussian blue reaction indicated pernicious anæmia as well, however.

Date.	Red corpuscles per cent. of normal.	Hæmoglobin.	Colour index.	White corpuscles per cub. mm.
	Thoma Ziess.	Fleischl.		
22 March, 1891	20	20	1·0	Normal

The post-mortem examination showed :—

Some slight œdema of the feet, ankles, and legs.

A small, firm, but wasted brain.

A heart weighing ten ounces, pale in colour, and soft, with evidence of both fatty degeneration and fatty infiltration ; no pericarditis, although during life the bruit de galop had been well marked.

The stomach, intestines, and lungs looked natural.

The liver weighed fifty-seven ounces, and gave a well-marked Prussian blue reaction. For comparison, the livers of two other cases examined post-mortem the same afternoon—one a case of granular kidney, the other one of lobar pneumonia—were tested in precisely the same way, and gave no similar Prussian blue reaction.

The gall bladder contained two small gallstones.

The spleen weighed four ounces ; it was pale, but firm.

The kidneys were pallid, and microscopically exhibited some fatty degeneration of the epithelial cells, but no nephritis and no interstitial fibrosis.

There is no mention of the bone marrow, nor of the Prussian blue reaction in spleen or kidneys.

The temperature chart was as follows :—
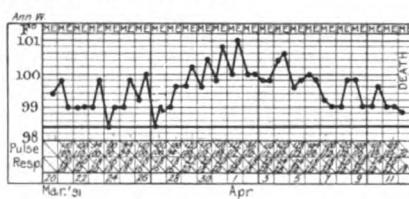
CASE 5.—Ref. No., Vol. 123, No. 106.—George B., æt. 57, a provision dealer's shop assistant, was in Clinical Ward from February 25th, 1891, to March 8th, 1891, and he had also been an in-patient in October, 1890, for what was probably part of the same disease. He gave the history that when he was 13 years of age he began to have attacks of pain in the abdomen, accompanied by diarrhœa, these attacks having recurred at intervals, especially in the summer time, when, for two or three weeks at a stretch, he would pass six or seven motions a day. At other times he would be constipated and suffer from "bilious attacks" accompanied by actual vomiting. It was very difficult to say what relation these attacks had to the pernicious anæmia; especially as the man was in the habit of taking too

much alcohol, and also had a stricture. He stated that he had been getting weaker and weaker for five or six years past, but till six months ago his only symptoms were diarrhœa, dyspepsia, and muscular weakness ; since then giddiness and a sensation of something pumping inside his head had been added ; and he has been getting very pale, and so weak that he could not exert himself physically at all. If he tried to do anything, moreover, he became extremely short of breath. He was " an averagely plump man," weighing 10½ st., but very pale, or rather primrose yellow. The urine was often dark ; it contained neither albumin nor blood. There was no œdema of the legs. There was a blowing systolic bruit, deemed to be hæmic, audible at the impulse, but not in the pulmonary area. No bruit de diable was heard. The cardiac impulse was in its normal position. The tongue and mouth were clean, but pallid. Neither spleen nor liver was palpable. Retinal hæmorrhages had been observed in 1890. The temperature was seldom over 99° F. He was discharged for rudeness to the nursing staff, and he has not been traced since. Only one blood count had been made ; it showed :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
February, 1891	1 400,000	34	35	1·029	—

No temperature chart is available in this case.

———

CASE 6.—Ref. No., Vol. 126, No. 155.—Louisa H., æt. 41, a married woman, was in the hospital under the care of Dr. Goodhart from March 8th, 1892, to April 20th, 1892, and went out for family reasons, although she was in an almost dying condition at the time. Her actual fate is not known. Her illness began a month before her admission with loss of appetite, languor, shortness of breath, and general weakness, all of which symptoms came on gradually, but steadily increased. She had had no vomiting and no diarrhœa. When she got about there was some œdema of her ankles and legs. She was a stout woman, and had a very pale yellow colour. Her liver extended three inches and the spleen two inches below the costal margin. The urine was dark coloured, but contained no albumin, blood or sugar. Urobilin was not mentioned. The lungs were natural, and the heart was of normal size, but presented systolic hæmic bruits both at the impulse and in the pulmonary and the aortic areas. The optic discs were normal. The patient's temperature was normal in the morning, but rose to about 100 or 100·6° F. every night throughout her stay in the hospital. The pulse rate varied from 92 to 120, and the respiration rate from 20 to 44. Ascites developed, apparently as the result of a "simple" peritonitis, measurements at the level of the umbilicus being as follows :—

March 14th ...	... 39½ inches.		March 19th ...	... 42 inches.	
„ 17th ...	... 41½ „		„ 21st ...	... 42 „	
	April 4th ...	... 45 inches.			

Although more than one blood count was made in this case, the only one of which there is a record is the following:—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
12 March, 1902	800,000	16	18	1·125	—

The temperature chart was as follows:—
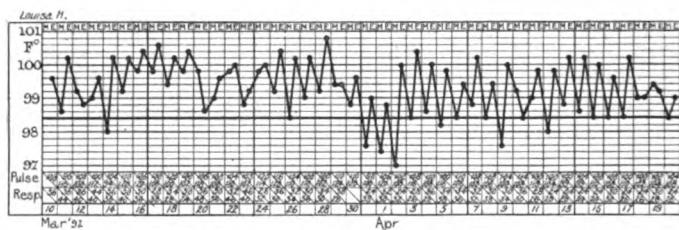
CASE 7.—Ref. No., Vol. 127, No. 158.—Stephen M., æt. 44, a cooper, was in Guy's Hospital from August 25th to September 22nd, 1892. A letter, dated August, 1907, from 14, Horne Gardens, Dartford, states that "Mr. Stephen M. died on February 11th, 1901." He gave the history that at 19 he suffered from severe diarrhœa for some weeks, and his doctors were in much doubt as to whether he had not had typhoid fever. Since then, as he himself expressed it, "every little thing seemed to cause diarrhœa." For some years he had also been subject to severe neuralgia. For three or four years before admission, in 1892, he had been much subject to what he termed "bilious attacks," in which he retched more than he vomited. He had also latterly noticed himself gradually losing colour and strength. He had had an exceptionally severe bilious attack, which laid him in bed for twelve weeks during January, February, and March, 1892. After this he returned to work, but he gradually became so weak that he could not continue. His friends described him as "jaundiced," remarking upon his yellow colour, but neither the conjunctivæ nor the urine exhibited bile pigment. The body was in a condition of general flabby fatness rather than of wasting. There was some tenderness over the long bones, such as the tibiæ and humeri. The tongue was clean, but the teeth were in a bad state. The spleen could not be felt. The liver could be palpated just below the ribs. The heart was not enlarged, but it presented systolic bruits at the impulse and in the pulmonary area, in addition to a bruit de diable in the neck. The lungs presented no abnormal physical signs. There was much pain in the right flank and in the back. Perhaps this was due to the same cause as the tenderness in the long bones, namely, changes in the bone marrow. The urine contained both indican and urobilin, but no albumin, except upon a single occasion. There were no hæmorrhages; the optic discs were normal; the pulse rate averaged 82; the

temperature rose to 99° F. or 100° F. every night. The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Leitz.		Haldane.		
27 August, 1892...	2,750,000	55	—	—	—
3 Sept., "	2,200,000	44	40	0·909	—
8 " "	2,560,000	51	50	0·980	—
12 " "	2,650,000	53	48	0·906	—
16 " "	2,400,000	48	56	1·166	—
20 " "	2,500,000	50	50	1·000	—

Note.—Poikilocytosis. Nucleated red corpuscles were present, and there were many megalocytes and microcytes.

The temperature chart was as follows :—
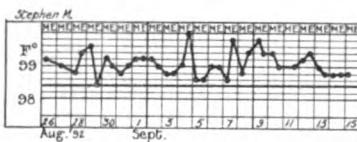
CASE 8.—Ref. Nos., Vol. 125, No. 121, and Vol. 136, No. 27.—Anne G., æt. 51, was admitted under Dr. Taylor on November 14th, 1892, to be discharged relieved on December 10th, 1892. She relapsed and was re-admitted under Dr. Hale White on March 18th, 1893, to be discharged relieved on May 3rd, 1893, relapsing again and being re-admitted December 19th, 1893, and re-discharged on January 24th, 1894. The husband reported, upon inquiry, that she died of her complaint on August 26th, 1894. It is noteworthy that although each time she was discharged she felt better than when she was admitted, the blood condition itself showed comparatively little improvement throughout the time she was under observation. She was a married woman whose menopause had occurred when she was 47, since which time she complained of having become progressively weaker. Exactly when her illness began she could not say, but the history was an indefinite and long one as follows :—At twenty-five years of age, when she was in Constantinople, she had a severe attack of abdominal pains and diarrhœa, which was diagnosed as "cholera," since which attack she had been regularly subject to "Summer diarrhœa, alternating with constipation, bilious attacks, and headaches." She had also suffered from attacks of what she termed "low fever," lasting from seven to fourteen days at a stretch. Since her menopause in 1888 she had been languid and unfit for exertion, and short of breath after doing anything. She was of the typical lemon yellow colour, did not complain of loss of weight, and was fairly well nourished. The heart was of normal size, but there was a systolic hæmic bruit at the impulse and in the pulmonary and aortic areas. There was also a venous hum in the neck. The lungs were natural. The urine was of a light red colour; it contained a trace of albumin most of the time she was in hospital, very

little indican, and sometimes no urobilin, sometimes plenty. The nervous system was natural as regards its reflexes, but there was great muscular weakness in the legs and arms. There were upon occasions purpuric spots upon the abdomen, chest and legs, but no retinal hæmorrhages, and no visceral bleedings. The spleen was enlarged and very firm, coming well below the ribs. The liver could just be felt. The temperature chart was a typical one, reaching 100°F. to 101°F. every evening, falling to 97°F. every morning. Arsenical treatment was adopted, and it is noteworthy that on April 17th, 1893, she developed an extensive eruption of supra-orbital herpes. The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
21 Nov., 1892 ...	1,050,000	21	14	0·666	—
24 „ „	1,050,000	21	18	0·857	—
7 Dec., „	1,050,000	21	25	1·190	—
18 March, 1893...	750,000	15	19	1·266	—
21 „ „	750,000	15	19	1·266	—
25 „ „	850,000	17	20	1·177	—
29 „ „	950,000	19	17	0·894	—
4 April, „	1,050,000	21	25	1·190	—
10 „ „	1,300,000	26	30	1·154	—
17 „ „	1,280,000	25	28	1·120	—
27 „ „	1,500,000	30	30	1·000	—
3 May, „	1,450,000	29	33	1·139	—
21 Dec., 1893 ...	850,000	17	20	1·177	—

Note.—Films repeatedly showed large numbers of poikilocytes, microcytes, and megalocytes. There was no remarkable number of nucleated red corpuscles.

The temperature chart was as follows :—
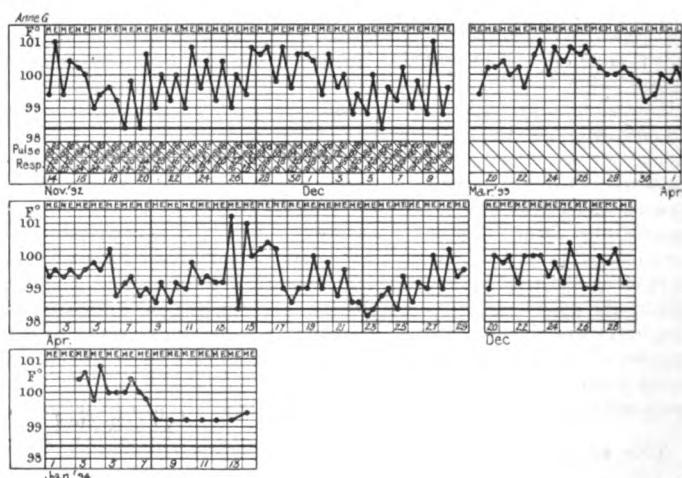
CASE 9.—Ref. No., Vol. 129, No. 130.—Charles R., æt. 22, a clerk, was in the hospital, under Dr. Pye-Smith, from January 20th, 1893, to the 22nd March, 1893, and he died two weeks after his discharge. He was described as being "the drunken son of a drunken father." He came in for paralysis of his legs, all the muscles in them exhibiting the reaction of degeneration. His condition was one of extreme peripheral neuritis due to alcoholism, and at the same time there was an extreme degree of anæmia of the typical pernicious type. It was stated that the trouble began two months before admission, with cramp in the legs and numbness. There had been no gastric symptoms and no diarrhœa. The teeth were in excellent condition. Neither the liver nor the spleen could be felt. The heart was of normal size, but exhibited hæmic systolic bruits at the impulse, in the pulmonary and aortic areas, and in the veins in the neck. The urine was of a dark colour, and it precipitated uric acid crystals; it was doubtful whether it contained urobilin. There were retinal hæmorrhages in both eyes. The pulse rate was usually about 100, and the temperature reached 101° F. each evening during the first three weeks of the patient's stay, and during the latter part of his stay reached from 99 to 100° F. each night. The patient's general colour was of a typical lemon yellow of pernicious anæmia. The blood counts were as follows:—

Date.	Red corpuscles, per cub. mm.	Red corpus-cles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
18 February, 1893	600,000	12	12	1·000	—
24 „ „	700,000	14	20	1·428	—
7 March „	1,500,000	30	30	1·000	—

Note.--On March 7th, 1893, the alkalinity of the blood was equal to 150 mgrm., KOH. (Hunter).

The temperature chart was as follows:—
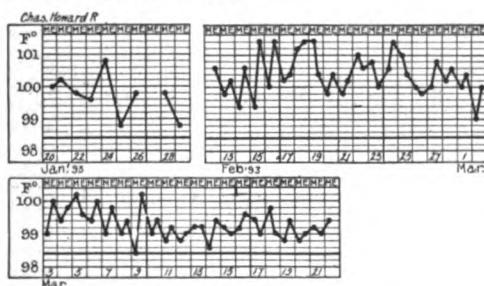
CASE 10.—Ref. No., Vol. 132, No. 158, and Post-mortem No. 224, 1893. (See Museum Specimen No. 133.)—Richard F., æt. 55, a fish dealer, was admitted under Dr. Hale White on March 8th, 1893, for anæmia, short-ness of breath, and weakness, and died on June 17th, 1893. Briefly, he was a syphilitic drunkard, who had none the less been in what he termed good health until about eight weeks before his admission; he then first noticed a languor in his legs on going upstairs, and there had been a rapid and

progressive increase in this loss of strength. There had been no vomiting and no diarrhœa. He became too weak to be out of bed. There was loss of weight down to 8st. 9lbs., but much less loss of bulk. On admission he presented the typical lemon colour with a reddish flush over each malar bone. There were hæmic bruits all over the precordial area, loudest at the impulse. The teeth were in excellent condition, only two were missing. The liver could be felt, firm, but smooth, three-quarters of an inch below the ribs. The spleen was not felt. There were retinal hæmorrhages in each eye. The knee-jerks were absent, though the pupils reacted normally. The urine had a specific gravity of 1012, it contained neither albumin nor blood, but both indican and urobilin were abundant on occasions. The alkalinity of the blood was normal. Arsenic was ill-tolerated in that it caused incessant diarrhœa. Towards the end the patient was very drowsy, with Cheyne-Stokes respiration for several days. The liver enlarged rapidly so as to reach almost to the umbilicus, pericarditis developed, and the patient died comatose. At the autopsy the marrow of the tibiæ was deep red ; the brain exhibited several ochreous depressed patches in the cortex, apparently the result of former hæmorrhages ; none of these patches were very large, but they were quite numerous ; the arteries were healthy ; there were fifteen ounces of clear serous fluid in either pleural cavity, the lungs and pleuræ being healthy ; the heart exhibited marked tabby-cat striation, and acute plastic pericarditis; the alimentary canal seemed natural ; the liver was firm and pale, and it gave a very marked iron reaction both with the potassium ferrocyanide and with the ammonium sulphide tests ; the kidneys together weighed thirteen and a half ounces, they were pale, and gave a marked ferrocyanide reaction in streaks ; the spleen weighed ten ounces, and it gave a slight ferrocyanide reaction ; the pancreas was tough to an unusual degree. The temperature chart and the blood counts are appended ; it will be noticed the temperature was slightly but constantly raised each evening to something between 99°F. and 100·4°F.

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Zeiss.		Gowers.		Thoma Zeiss
8 March, 1893	1,200,000	24	18	0·750	No leuco-
10 " "	1,000,000	20	16	0·800	cytosis
14 " "	1,050,000	21	15	0·714	——
17 " "	1,000,000	20	20	1·000	—
21 " "	1,550,000	31	30	0·968	—
25 " "	1,350,000	27	25	0·926	—
29 " "	1,200,000	24	27	1·125	—
3 April "	600,000	12	10	0·833	—
5 " "	750,000	15	20	1·333	—
7 " "	750,000	15	22	1·466	—
11 " "	600,000	12	24	2·000	—
14 " "	1.500,000	30	22	0·733	—
18 " "	1,500,000	30	25	0·833	—
2 May "	2,250,000	45	30	0·666	—
6 " "	1,800,000	36	30	0·833	—
9 " "	2,250,000	45	32	0·711	—
13 " "	2,250,000	45	40	0·888	—
17 " "	1,900,000	38	40	1·053	—
22 " "	1,000,000	20	20	1·000	—
26 " "	2,000,000	40	35	0·875	——
30 " "	2,000,000	40	32	0·800	—
5 June "	1,750,000	35	20	0·571	—

Note.—Poikilocytes, megalocytes, and microcytes abundant. Nucleated red cells not strikingly abundant.

The temperature chart was as follows :—
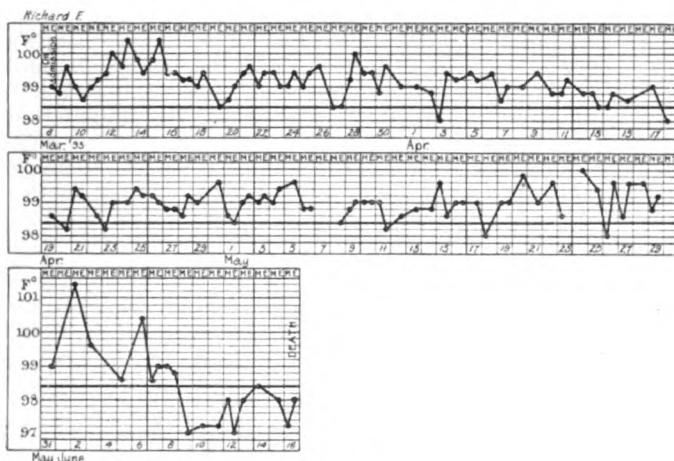
CASE 11.—Ref. No., Vol. 135, No. 6 ; Post-mortem No. 226, 1894. — Edward B., æt. 56; was admitted, under Dr. Goodhart, on May 24th, 1893, became relieved, and was discharged on July 22nd, 1893 ; he relapsed soon after, was readmitted on November 20th, 1893, and died on June 9th, 1894. He gave the history that he was quite well until five years before his first admission, and that he then suffered from a bad attack of diarrhœa during the summer, losing much blood per rectum at the time ; each summer since then he had had a precisely similar and very severe attack. In March, 1892, he first thought he was "jaundiced," and told his doctor so. In July, 1892, he was so much worse that he was laid up in Croydon Hospital for twenty-two weeks. After that he worked for eight weeks, but became progressively weaker and more ill. He had suffered from pains in the chest and abdomen and from giddiness for over two years. These, together with prostrating weakness, were his main symptoms on admission. He was the typical colour. There had only been slight loss of weight. He was 11 st. 1 lb. on admission. His temperature was always at least 99° F. at night, often it was 100° F., and sometimes 101° F. There were well-marked retinal hæmorrhages and hæmic bruits. There had been œdema of the ankles, but this was gone when he lay in bed. Appetite was poor, but there was no vomiting. The fæces were small and very hard globular masses, looking "like iron rust." The spleen was not felt now, but it was ultimately quite large. The liver was felt down to the umbilicus or lower. The urine had a specific gravity of 1010, and it was constantly pale ; it deposited uric acid crystals ; it contained neither albumin (except once) nor blood, and urobilin was absent to the ordinary spectroscopic test. There were subcutaneous petechiæ upon the arms and diffuse purpuric blotches on the legs. Epistaxis also occurred spontaneously more than once. After the administration of arsenic there were one or two severe diarrhœic attacks. Itching of the skin was at one period

a very troublesome symptom, though jaundice was entirely absent. During the final relapse the patient became œdematous, and serous exudations occurred. Finally, there was increased pyrexia, with rigors, due to a terminal infective endocarditis, which was the immediate cause of death. The post-mortem examination showed : A well-nourished body, profoundly anæmic, with yellow fat, and some œdema of the nether limbs. Each pleural cavity contained three pints of serous fluid ; the pericardium contained eighteen ounces of similar fluid, and the peritoneum forty-one ounces. The lungs were very pale and extremely œdematous. The alimentary canal looked natural. The heart was pallid, the mitral and pulmonary valves were œdematous, the former being incompetent and the latter bearing acute granulations near îts free edge. The spleen weighed nineteen ounces, and was dark and tough, the kidneys weighed thirteen ounces, and the liver eighty ounces; liver, spleen and kidneys all contained a large excess of iron, and gave a well-marked Prussian blue reaction. The blood counts made during life were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Zeiss,		? Method.		
24 May, 1893	800,000	16	30	1·875	No leuco-cytosis
5 June „	1,250.000	25	35	1·400	—
20 „ „	2,100,000	42	50	1·190	—
7 July „	1,850,000	37	45	1·216	—
21 . „	2,750,000	55	60	1·091	--
15 January, 1894	500,000	10	18	1·800	—
28 „ „	1,150,000	23	—	—	—
6 February „	900,000	18	20	1·111	—
7 March „	1,000,000	20	20	1·000	—
22 „ „	900,000	18	18	1·000	—
10 April „	1,250,000	25	20	0·800	—
4 May „	1,600,000	32	15	0·469	—
29 „ „	2,000,000	40	30	0·750	—
8 June „	1,850,000	37	19	0.514	—

Note.—The red cells in film were typical of pernicious anæmia.

The temperature chart was as follows :—
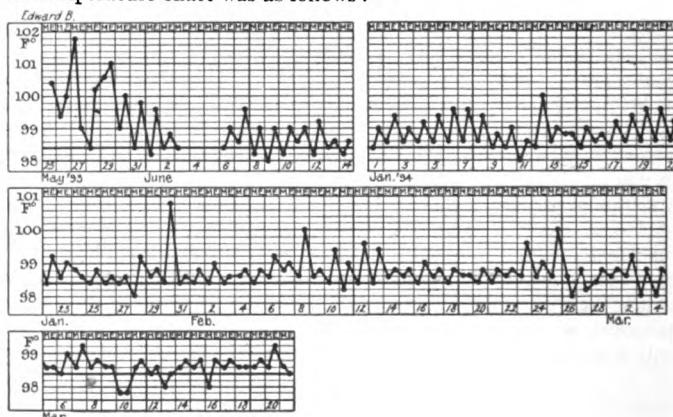
CASE 12.—Ref. No., Vol. 130, No. 143.—John F., æt. 52, a curator
of a Miners' Institute in Durham, was admitted for "general debility and
anæmia" under Dr. Taylor on September 14th, 1893, and was discharged
relieved on October 3rd, 1893. He had always enjoyed good health until four
years previously, when he began to suffer from giddiness, occipital headaches,
and impaired appetite; and he noticed that he very readily became fatigued.
These symptoms increased slowly but progressively. Two years before
admission he had "coughed up" eight ounces of blood, but there had been no
further pulmonary symptoms. On admission he was a fairly typical case of
pernicious anæmia. Neither liver nor spleen could be felt. The lemon
yellow colour of skin was distinctive. The heart sounds were normal. The
urine had a specific gravity of 1020; there was neither albuminuria nor
hæmaturia. Arsenical treatment afforded some relief; but Alice F. writes
on August 15th, 1907: "John F., after leaving Guy's Hospital, was in greatly
improved health, and his friends all noticed a great change; but the following
winter he contracted a severe attack of influenza, which again brought on the
old complaint. . . . He died on July 25th, 1894." The blood count was as
follows:—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Zeiss.			Gowers.	
20 Sept., 1898 ...	1,500,000	30	50	1·666	—

No temperature chart is available in this case.

CASE 13.—Ref. Nos., Vol. 136, No. 15; Post-mortem No. 62, 1894.—
Samuel D., æt. 45, was admitted under Dr. Hale White on December 23rd,
1893, and died on February 9th, 1894. He gave a history of having been
dangerously ill six years previously with symptoms which were diagnosed as
"cholera," though he had never been abroad. He recovered after some
while, and enjoyed fair health for five years. He then began to get pro-
gressively weaker, to lose his appetite, to suffer from very troublesome
diarrhœa, and from breathlessness on ordinary exertion. He had been
continuously under medical treatment from August, 1893. His height was
5ft. 5ins., and his weight 8st. His skin had the lemon colour of pernicious
anæmia. There were hæmic bruits in the mitral, aortic and pulmonary
areas, and in the neck. Neither liver nor spleen could be felt. The urine
was dark, and contained both indican and urobilin, but neither albumin,
blood, nor sugar. The optic discs and retinæ were at first natural, but later
they developed hæmorrhages. Much diarrhœa interfered with arsenical
treatment. There was a very slight improvement for a time, then a relapse,
and the patient lay semi-comatose for some days before he died. There was
no œdema. The lymphatic glands were not obviously abnormal. The lungs
and pleuræ were natural, except for old adhesions over the latter, and petechial
hæmorrhages both under the pleura and within the lungs. The heart
weighed twelve ounces; the valves were natural, but the muscle exhibited
some degree of tabby-cat striation. The stomach and intestines all looked
quite natural; there were not even any enlarged follicles in the colon. The
liver was pale brown and gave a moderately good Prussian blue reaction with

the potassium ferrocyanide test. The spleen weighed seven ounces; it was firm and dark. The kidneys together weighed nine ounces; they were anæmic, but otherwise seemed healthy. The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Zeiss.		Gowers.		
21 Dec., 1893 ...	1,000,000	20	17	0·850	—
1 January, 1894	1,200,000	24	20	0·833	—
19 „ „	1,450,000	29	24	0·827	—
26 „ „	850,000	17	25	1·470	—

The temperature chart was as follows :—
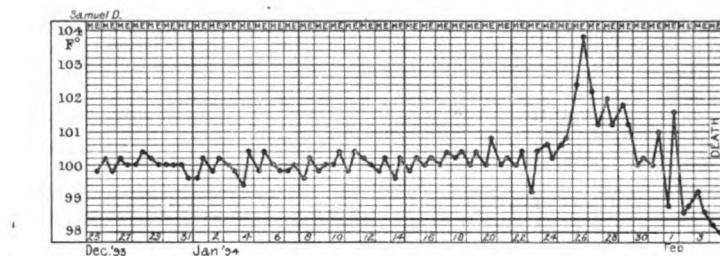
CASE 14.—Ref. Nos., Vol. 136, No. 352, and Vol. 194, No. 26.—James F., æt. 60, an Army pensioner, was admitted for diarrhœa, weakness, and tingling in fingers and toes, under Dr. Hale White, on January 4th, 1905, and he was discharged relieved on January 28th, 1905. He had been in Guy's Hospital in 1894 for very much the same symptoms, and at that time he had been ill for seven months with loss of appetite and strength, and the frequent passage of small quantities of blood per rectum. At that time he was very anæmic indeed, the red corpuscles numbering only 30 per cent. of the normal, but neurotic dyspepsia was diagnosed, and the anæmia was attributed to the loss of blood per rectum. A very thorough rectal examination was made under an anæsthetic, but the source of bleeding could not be found; colitis was suspected, but not actually diagnosed. Treatment was by means of iron and arsenic together, and the patient was discharged, greatly improved in health, though weighing only 8st. 9lbs. He maintained his improved health for *over ten years*, and by November, 1904, he weighed 13st. 7lbs. He now began to feel ill again, with loss of appetite, weakness, and diarrhœa. The latter occurred to the extent of fifty motions a week at one period, though at the time of readmission there were only two or three motions a day. There was no vomiting, and there was now no blood loss in the stools. A fortnight before he was admitted his old tingling of fingers and toes began to trouble him again. He was extremely yellow, but not jaundiced, with plenty of subcutaneous fat and a flush over each malar bone. The lungs were natural. The heart was of normal size, but presented a hæmic bruit. The teeth were good, and the mouth clean and sweet. The spleen was not felt. The liver could be palpated one inch below the ribs. The

reflexes were natural, but there were sensory disturbances n the form of acroparæsthesia. The urine was acid, and of specific gravity 1014; it contained neither pus, blood, nor albumin ; urobilin is not mentioned. The chart shows a very slight but repeated rise each evening. The pulse rate varied from 76 to 100, and the respiration rate from 18 to 24. The subsequent history of the case is given by his daughter, as follows (August 14th, 1907):— " Dear Sir,—With reference to your letter. . . . I think you already know my father's illness in 1895 was succeeded by a second of exactly similar nature in 1905, and that on both occasions he was an in-patient at Guy's. He left hospital in January, 1905, and for three or four months maintain d fair health, though less strong than he had been. About May, 1905, he showed signs of increasing weakness, loss of appetite, and frequently com-plained of deadness in his finger tips. He was able to keep about till the end of June, 1905, when he died very suddenly, death being due to an apoplexy of the brain. This last illness extended little over twenty-four hours, during which he was unconscious. . . . " The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpus-cles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Leitz.		Haldane.		
5 January, 1905	2,500,000	50	53	1·060	—
18 „ „	2,000,000	40	46	1·150	8,500
25 „ „	3,370,000	67	56	0 836	—

Note.—Films showed many poikilocytes and megalocytes.
The temperature chart was as follows :—
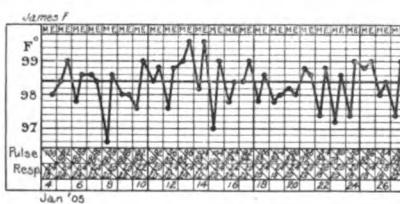
CASE 15.—Ref. No., Vol. 146, No. 65.—Albert H., æt. 26, an ex-soldier, was admitted to the hospital, under Dr. Goodhart, on February 3rd, 1896, and was discharged relieved on April 6th, 1896; after that he could not be traced. He came in for general weakness and shortness of breath on exertion, and gave the history that he was perfectly well until he was stationed at Aden, in 1890. There he felt ill and weak and unable to work, so he returned to India on sick leave. He thought he had had no fever until 1893. He returned to England in February, 1895, being invalided to Netley. His health improved, and he was discharged much better. In August, 1895, he began to get weak again, listless, and disinclined to work. He lost his appetite, and his doctor kept him in bed for six weeks, and his health was much improved again by October, 1895. He tried to work in the Arsenal, at Woolwich, but he got weaker again, and short of breath on walking. By the day of his admission he was so weak that it was a misery for him to go out

of doors. He was a tall man, profoundly anæmic, not wasted apparently, but thinner than he had been. The heart was of normal size, but it exhibited hæmic systolic bruits at the impulse and in the pulmonary area. The lungs were natural. The tongue was clean, and the teeth were noted as being exceptionally good. The bowels were open regularly. Neither liver nor spleen could be felt. There was no vomiting. The urine was a light colour, having a specific gravity of 1020, and it contained no albumin nor any blood. It occasionally exhibited urobilin to the spectroscopic test. There were no retinal hæmorrhages. Sensation was normal. The knee jerks were absent. There was a general brown pigmentation of the skin, but none of the mucous membranes. Treatment was by means of arsenic. Previous to the patient's discharge the spleen could be felt below the costal margin. The temperature was sometimes as high as 102° F., and always at least 99° F., at night, and often between 99° and 100° F. The patient's weight was 10st. 5lbs., with clothes. The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
4 February, 1893	650,000	13	30	2·308	—
22 „ „	600,000	12	20	1·666	—
3 March, „	1,000,000	20	27	1·350	—
7 „ „	1,650,000	33	28	0·849	—
14 „ „	3,100,000	62	33	0·532	—
21 „ „	2,950,000	59	37	0·627	—
28 „ „	3,600,000	72	52	0·722	—
7 April „	3,500,000	70	75	1·071	—

The temperature chart was as follows :—
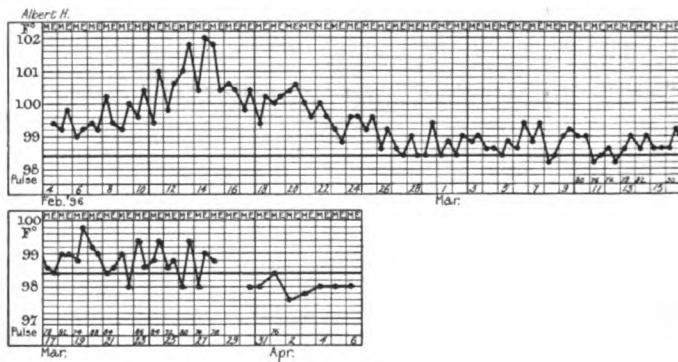
CASE 16.—Ref. No., Vol. 148, No. 345.—Henry N., æt. 61, an engineer's assistant, was admitted under Dr. Hale White on 15th September, 1896, and was discharged, relieved to some extent, on October 27th, 1896. He remembered no illness until three years previously, when he found he began to get very easily tired. This physical weakness increased slowly, but persistently, until he was unable to ascend even two or three steps. He also experienced

subjective sensory symptoms, which he described as "tearing pains in his chest and abdomen, and feeling as though his body were being tightly gripped and squeezed." The skin was the typical yellow colour. The muscles were flabby, but there had been only slight loss of bulk. The body weight was 9st. 11lbs., without clothes. The ankles were a little œdematous. The pulse rate averaged 60 to 80, the respiration rate 16 to 32, and the temperature was often 99° F. at night, though it never exceeded 99·8° F. There were pigmented scars upon his legs and petechiæ under the skin on the backs of his hands. The heart presented no bruit. The urine had a specific gravity of 1020, and contained neither blood nor albumin, but gave a urobilin band spectroscopically. The spleen was palpable, the liver was not. The patient was edentulous. The nerve reflexes were natural. The patient at no time suffered either from vomiting or from diarrhœa. Arsenical treatment was adopted. Since his discharge he has not been traceable. The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Zeiss.	*			
15 Sept., 1896	575,000	12	15	1·250	No leuco-
16 „ „	600,000	12	15	1·250	cytosis.
22 „ „	850,000	17	25	1·470	—
29 „ „	1,500,000	30	25	0·833	—
2 Oct. „	1,350,000	27	25	0·926	—

Note.—Megalocytes and poikilocytes were numerous.

* The figures in the report are double; as indicated by the figures for October 2nd in the original, the calculations had been erroneous.

The temperature chart was as follows :—
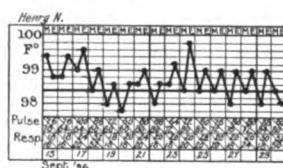
CASE 17.—Ref. No., Vol. 145, No. 306 ; Post-mortem No. 448, 1896.— Caroline L., æt. 50, was admitted on October 23rd, 1896, under the care of Dr. Perry, and she died on November 2nd, 1896. She was a married woman who "had never been strong." In 1889 she had had a bad attack of "English cholera," and since then she had been continuously weak, liable to sweating attacks both by day and by night, and she had had to be extremely careful with her eating, or else she suffered from abdominal attacks associated with diarrhœa. On July 20th, 1896, she was suddenly attacked with acute vomiting, since when she had often been actively sick eight and ten times a day. She had lost flesh slightly, and she had become very giddy. She was a fairly well-nourished person, very anæmic, with typical pale yellow skin and white conjunctivæ. The heart presented hæmic bruits in all areas,

but particularly at the impulse. Her throat felt "parched," and the tongue
was sore. There were streaks of blood with the motions. The liver was
palpable just below the rib margin, and there was a sense of resistance over
the splenic area, though the spleen was not actually felt. There were rhonchi
audible over both lungs. The temperature was at first up to 105·6°F., later
it reached 100°F. or 101°F. almost every evening, and the pulse rate lay
between 96 and 120, and the respiration rate between 20 and 36. The urine
was high coloured, and it contained a trace of albumin, but no blood.
Urobilin, indican, and renal tube casts are not mentioned. There were no
obvious retinal hæmorrhages. The nervous system did not seem abnormal
clinically, though changes in the posterior columns were found post-
mortem. The patient died of progressive weakness and exhaustion. The
blood count showed no high colour index; but the post-mortem findings
were pathognomonic.

Date.	Red corpuscles, per cub. mm.	Red corpus-cles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index	Leucocytes per cub. mm.
	Thoma Zeiss.		Fleischl.		
27 October, 1896	1,200,000	25	15	0·600	No leuco-cytosis.

Note.—Poikilocytes very numerous.

The body was fairly well nourished, but extremely pallid—pale yellow.
The brain weighed fifty-one ounces, and appeared normal macroscopically.
The pia-arachnoid over the cervical and upper dorsal region of the spinal cord
was curiously pigmented, of a dark grey colour; and there was also definite
degeneration in the posterior columns :—
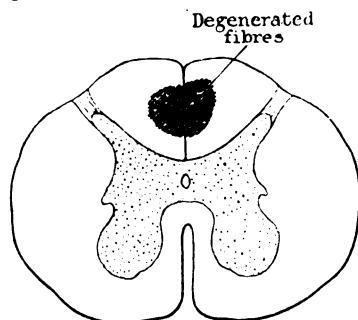
The spinal degeneration was confirmed microscopally.

The lungs were pale and œdematous ; there were a few pleural adhesions,
but no active pleurisy. The heart weighed ten ounces. Its valves and
pericardium were normal, but the muscle exhibited well-marked tabby-cat
striation. The alimentary canal exhibited neither gastritis nor enterocolitis.
There was no ascites. The liver weighed fifty-one ounces, was of the
typical café-au-lait colour, and gave a deep Prussian-blue reaction to
Perl's test. The spleen was large and pulpy, weighing fourteen ounces.
The kidneys together weighed ten ounces, and they gave a considerable iron
reaction also. The bone marrow was not mentioned.

The temperature chart was as follows :—
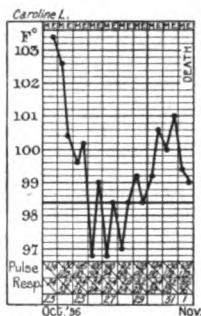
CASE 18.—Ref. No., Vol. 155, No. 242.—William D., æt. 66, a carpenter, was admitted under Dr. Taylor on September 7th, 1898, and discharged relieved on October 25th, 1898. He came in for weakness, precordial pain, and anæsthesia of his feet. He had been exceptionally strong and well until six months previous to admission, and then weakness and languor began to creep over him, and he used to suffer from pain over his heart on any exertion, such as that of trying to carpenter. He "could not feel sure of his foothold owing to numbness in his soles, so that he used to stumble like a drunken man sometimes." Occasionally there was œdema of the ankles when he had been standing, and he was short of breath on doing anything. He had lost weight, but not bulk, and his tissues felt to him soft and flabby. He weighed 130 pounds. The heart dulness extended out to the left nipple line, and there were hæmic bruits both at the apex and at the base and at the root of the neck on either side. The pulse rate was usually about 72. The temperature did not exceed 99° F. The knee-jerks were natural. The urine was very pale, of specific gravity 1008 ; it contained neither albumin nor blood. The discs and retinæ were natural; neither liver nor spleen could be felt. The teeth were in very fair condition. There was diarrhœa after arsenic had been given, but none before. After rallying he went out, and his wife reports (August, 1907), "Mr. D. has been dead seven years. He was ill for two years after leaving Guy's and died of heart failure." The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Zeiss.		Gowers.		
8 Sept., 1898	900,000	18	32	1·777	—
9 " "	900,000	18	28	1·555	—
13 " "	1,450,000	29	40	1·380	—
20 " "	2,000,000	40	38	0·950	—
24 " "	1,950,000	39	40	1·026	—
30 " "	2,250,000	45	65	1·444	—
12 October "	4,500,000	90	45	0·500	—
16 " "	4,500,000	90	45	0·500	—
21 " "	4,500,000	90	60	0·666	—
24 " "	4,500,000	90	65	0·722	—

The temperature chart was as follows:—

William D

99
98
97

Sept.'98   Oct.
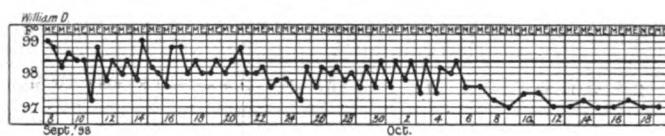
CASE 19.—Ref. No., Vol. 156, No. 380.—Alice D., age not known, was admitted for weakness, flatulence, and pain over the heart, under the care of Dr. Taylor, on November 5th, 1898, and she was discharged relieved on December 30th, 1898. Attempts to trace her since then have failed. She was a married woman who had always suffered from "indigestion." Otherwise she had been perfectly well until her first miscarriage "some years ago," when she lost a great deal of blood, and since when she had always been ailing more or less. "Last year" she was in bed for three weeks with giddiness and dyspepsia. She dated the illness for which she was admitted to the middle of August, 1898, when she became so physically weak and languid, and suffered so from the "spasms," that by doctor's orders she stayed in bed. Since that time she had suffered from œdema of the feet whenever she got up. She was very anæmic and thin, weighing only 5st. 4lb. Neither liver nor spleen could be felt. A hæmic bruit was audible at the impulse and in both pulmonary and aortic areas. The urine nearly always contained obvious urobilin, but neither albumin nor blood. Improvement under arsenical treatment was rapid for the time being at least, though what has happened to the patient since is unknown. The blood counts were as follows:—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Zeiss.		Gowers.		Thoma Zeiss.
8 Nov., 1898	1,250,000	25	46	1·840	No leuco-
16 „ „	3,600,000	72	70	0·972	cytosis.
18 „ „	2,400,000	48	—	—	—
1 Dec., „	3,100,000	62	50	0·807	—
10 „ „	4,000,000	80	60	0·750	—
20 „ „	3,000,000	60	65	1·083	—

No temperature chart is available in this case.

CASE 20.—Ref. No., Vol. 157, No. 105.—William W., æt. 47, a coachman, was admitted under the care of Dr. Washbourn on March 9th, 1898, and was discharged relieved on April 30th, 1898. The symptoms for which he was admitted were weakness, numbness of the hands and feet, and some swelling of the latter. He stated that he had been perfectly well until eight months previously, when he began to experience a feeling of dizziness if he walked at all fast. Next he became troubled by swelling of the feet and ankles, starting in September, 1897; then by buzzing noises in his ears, great weakness, and numbness of his hands and feet. It was stated that he had also noticed blood in his urine, but the latter contained neither blood nor albumin during

his stay in hospital. There was no obvious urobilinuria. Neither spleen nor liver could be felt. The heart was of normal size; it presented a hæmic bruit in the pulmonary area. The optic discs were natural, and there were no retinal hæmorrhages. Arsenical treatment was followed by considerable improvement for the time being, but in reply to inquiries made in August, 1907, it was ascertained that "W. never recovered, but died about a year after he left the hospital." The temperature was at first 100° F. each night, but later, as improvement set in, it seldom exceeded 99° F. The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Zeiss.		Gowers.		Thoma Zeiss.
9 March, 1898	850,000	17	15	0·882	Normal
11 „ „	900,000	18	15	0·833	—
19 „ „	1,100,000	22	20	0·909	—
26 „ „	600,000	12	14	1·166	—
27 April, „	3,900,000	78	40	0·513	—

Note.—In stained films poikilocytes, megalocytes and microcytes were numerous, and there were a fair number of nucleated red cells.

The temperature chart was as follows :—
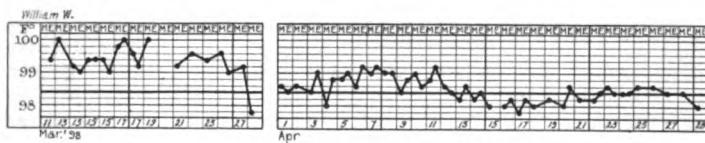
CASE 21.—Ref. No., Vol. 165, No. 74.—Annie T., æt. 37, a housewife, was admitted for œdema of the right leg and for a pustular eruption on the left leg, under Dr. Washbourn, on February 15th, 1900, and discharged, considerably relieved, on April 6th, 1900. Efforts to trace her since then have been unsuccessful. She stated that she had been perfectly well until four years previously, when she began to get weak, languid, and short of breath on exertion. She improved under her doctor's treatment. Attention had been called to the yellowness of her skin as long ago as that time. She had been subject to much vomiting, especially in the morning, although she had never been pregnant, and was not an alcoholic subject. There had been no hæmatemesis. Leucorrhœa was a considerable trouble to her. Her condition had been getting worse slowly for a long time. The swelling of her right leg was due to a recent thrombosis. The heart was not enlarged, but there were hæmic bruits in all areas. The teeth were all good. Neither liver nor spleen was felt. The urine was of a deep red-brown colour, and it contained much urobilin ; it had a specific gravity of 1018, and was free from albumin and blood. The pulse rate was about 92, respiration rate about 20, and the temperature often 99°, and once over 100° F. The only evidence of abnormality of the nerves was decided exaggeration of the

knee-jerks.   The patient's weight was 7st. 2lbs.   The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpus-cles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Zeiss.				Thoma Zeiss.
19 February, 1900	1,550,000	31	35	1·129	6,000
5 March „	2,250,000	45	50	1·111	2,000
17 „ „	3,300,000	66	65	0·985	2,000

Note.—Films showed many poikilocytes, megalocytes, normoblasts, and megoblasts. The differential leucocyte count on one occasion was as follows :*—S. 30, L. 8, P. 60, E. 5; on another it was S. 28, L. 2, P. 38, E. 2. No temperature chart is available in this case.

CASE 22.—Ref. No., Vol. 161, No. 209; Post-mortem No. 171, 1899.—Mary L., æt. 45, a laundress, was admitted under Dr. Pitt for progressive anæmia and for weakness, on May 26th, 1899, and died on May 30th, 1899. She said she had always been feeble, though she had had no more definite illness than "bad eyes," for which she was in Ruth Ward in 1882. Eleven months before her final admission she began to find walking very much harder than usual ; by degrees she got worse, and eight months ago nausea began to be very troublesome. Latterly she had found that the only way to avoid being sick after every meal was for her to lie down immediately after eating. This vomiting may, at least in part, have been due to arsenic which she had been taking regularly for some while. She was a stout-looking woman, not wasted, but profoundly anæmic and yellowish. The liver dulness came two inches below the costal margin, but the edge of the organ could not be definitely felt. The spleen was not felt. The urine had a specific gravity of 1,008, and it contained neither albumin nor urobilin so far as ordinary tests showed. The vomit contained no free HCl. There were retinal hæmorrhages. The patient became very restless, and shortly went into a coma, in which she died. Thirst and palpitations were occasionally prominent symptoms. The subcutaneous fat was abundant, and of the typical primrose yellow colour. The brain and spinal cord both seemed natural. The retinæ exhibited many small hæmorrhages. The lungs were œdematous, the pleuræ natural. The heart weighed fourteen ounces, exhibited many epicardial petechiæ, some excess of bright yellow superficial fat, and typical tabby-cat striations of musculi papillares; the fatty degeneration was confirmed microscopically. The stomach and intestines looked natural both to the naked eye and microscopically. There was no ascites. The liver weighed sixty-four ounces, was of the typical dull brown colour, and gave a very deep Prussian blue to the ferrocyanide test. The spleen weighed nine ounces. The left kidney weighed eight and a half ounces, being in a condition of compensatory hypertrophy on account of the right having been converted

      * *Note.*—S. = Small lymphocytes.
            L. = Large hyaline lymphocytes.
            P. = Polymorphonuclear cells.
            E. = Coarsely granular eosinophile cells.
            B. = Basophile leucocytes.
            M. = Myelocytes.

by a calculus, which was present, into a hydronephrotic bag weighing only one ounce. The pelvic organs were natural. The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
27 May, 1899	700,000	14	"Very low"	—	No leuco-cytosis.

Note. – Films showed marked poikilocytosis and megalocytosis, together with many nucleated red cells.

The temperature chart was as follows:—
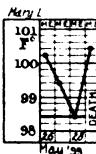
CASE 23.—Ref. No., Vol. 167, No. 32.—Marian E., æt. 53, a spinster and a dressmaker, was admitted under Dr. Perry on January 5th, 1900, and discharged, very greatly relieved, on May 30th, 1900. Her main complaint was of "loss of power in the legs." She had never been out of England. She stated that she had always been healthy until the last few years. Six years ago she had lost a great deal of blood per rectum; the cause was not clear. Two years ago she nursed a patient through scarlet fever, and after it she had symptoms that were diagnosed as "congestion of the lungs," from which she was ill seven weeks. Loss of power in both legs dated back for over a year previous to her admission. The weakness was due to lateral sclerosis, and it was so marked that the patient was quite unable even to stand. Six months ago she had an attack of severe vomiting and diarrhœa ; three weeks ago, involuntary micturition lasting a week. The diagnosis of pernicious anæmia was apparently made only after the nerve symptoms had been present for some time. On admission the skin was the typical pale yellow colour. The knee-jerks were exaggerated, there was ankle clonus on both sides, and the electrical reactions were normal. At the same time there were sensations of undue tingling in the hands and arms. There were brown pigmentary spots all over the patient, and latterly numerous petechiæ had appeared. There were no retinal nor other hæmorrhages. The heart was of normal size, but there were hæmic systolic bruits in the mitral and aortic areas and over the abdominal aorta. There was slight œdema of the ankles. The urine had a specific gravity of 1020; it was acid, contained no albumin and no blood, but an abundance of indican and also of urobilin to the ordinary spectroscope test. Both kidneys were palpable. The spleen was felt to be enlarged and firm, but the liver was not felt. The teeth were in only fair condition, but the mouth was clean. Vomiting and diarrhœa were marked symptoms at times, but possibly they may have been due to the arsenical treatment adopted. The pulse rate averaged 88 to 96, the respiration

ate 18 to 24. and the temperature was over 99° F. each day, and sometimes 100° F. Although the patient's blood became almost normal by the time of her discharge, the relief was but short-lived, the report received from the old address on August 15th, 1907, being that "Miss E. died in Hastings Hospital on October 10th, 1900" The blood counts were as follows:—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Zeiss.		Oliver or Fleischl.		Thoma Zeiss.
5 January, 1900	1,237,000	25	43 (Fl.)	1·720	5,000
16 „ „	1,250,000	25	40 „	1·600	3,125
24 „ „	1,855,469	37	40 „	1·081	3,125
21 February „	3,530,000	71	70 (Ol.)	0·985	—
9 March „	5,000,000	100	?	—	—
27 „ „	5,390,000	108	105 (Ol.)	0·972	4,130

Note.—Many poikilocytes and megalocytes. No nucleated red cells obvious.

The temperature chart was as follows:—
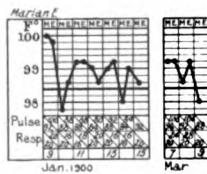
CASE 24.—Ref. No., Vol. 166, No. 206 ; Post-mortem No. 281, 1900.— James M., æt. 52, a Bombay merchant, was admitted for persistent diarrhœa and for general weakness, under the care of Dr. Pitt, on August 7th, 1900, dying on August 28th, 1900. He had been in India for thirty years, and had led the life of a strong athletic man. Twenty-five years ago he had had dysentery and bad hepatic trouble of some kind, but he recovered completely. As a young man he had had syphilis, but he was treated for "some time," and, so far as could be told, he had been cured. Latterly he had for some years been drinking heavily. His present symptoms dated back three and a half years previously to his admission. He stated that he got extremely wet on a journey up country, after which severe diarrhœa set in and never left him afterwards. Sprue was suggested. During the whole three and a half years he had never been free from troublesome diarrhœa, except for at most a day or two at a time. Very gradually he got weaker, and presently found it impossible to continue his work as a mercantile broker. He was in Bombay Hospital for six weeks, and it was from there that he was invalided home and came to Guy's Hospital. On admission he had a sallow complexion. The liver could be felt, the spleen not. The heart was of natural size, but exhibited a hæmic bruit at the impulse. There were subcutaneous hæmorrhages on the legs and back. The nervous system seemed natural. The urine was normal in colour, of specific gravity varying between 1008 and 1012 ; it contained a trace of albumin. The diagnosis at

first was "severe anæmia secondary to diarrhœa." A blood count later indicated pernicious anæmia, which was confirmed post-mortem. Towards the end the patient became light-headed, persistently getting out of bed before he gradually sank and died. The temperature was typically 99°F. to 100°F. nearly every day. The pulse rate varied from 84 to 104. Diarrhœa five times a day precluded the giving of arsenic, so that treatment was by opium, hæmatoxylin, and β-naphthol. Post-mortem, the heart, lungs, stomach, and intestines were recorded as natural. The liver was big, and gave a typical Prussian blue reaction, in addition to which it was in an early stage of cirrhosis. The spleen was large and soft. The kidneys were of a pale yellowish colour. There was apparently no œdema in this case. The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Leitz.				
16 August, 1900	600,000	12	30	2·500	5,000
24 „ „	1,000,000	20	—	—	3,800

The temperature chart was as follows :—
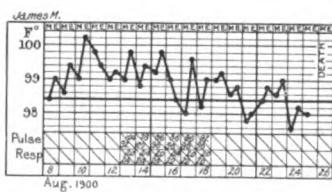
CASE 25.—Ref. No., Vol. 169, No. 272 ; Post-mortem No. 387, 1901.— Mary F., æt. 32, a market gardener, was admitted for general weakness under the care of Dr. Taylor on July 29th, 1901, and she died on October 21st, 1901. She was a married woman with two children, the youngest of whom was eight. She had never been out of England, and she had been perfectly well until about a year before her admission, when she began to feel weak and languid, with attacks of giddiness and faintness and pains in the sides and back. There appeared to have been neither diarrhœa nor vomiting. She was exceedingly weak and of the lemon colour, and she was described as "neurotic and hysterical." The whole body, except the face, was covered with petechial hæmorrhages, though there was no history of any other bleedings ; there had been amenorrhœa for seven months. The temperature chart shows the typical slight evening pyrexia continuously for three months. Both liver and spleen were palpable an inch below the ribs. The teeth were "in a very bad state." There was no tenderness of bones. The urine was turbid, of a pale amber colour, and specific gravity 1010 ; there was no albuminuria, but urobilin was found in abundance. The left knee-jerk was just obtainable, but the right was not obtained ; there was decided anæsthesia of all the finger tips. There was a marked bruit de diable in the neck, and later a bruit de galop at the cardiac

impulse, due to dilatation apparently, for there was pericarditis post-mortem. There was slight œdema of the ankles occasionally, and before death epistaxis occurred more than once. There was no rally, and the patient died of exhaustion, after becoming first extremely drowsy and then comatose. At the autopsy there was about a pint of serous fluid in each pleural cavity; the lungs and pleuræ were both healthy, except for the apical scarring of healed phthisis. The heart weighed 361 grams, and its muscle was brown, with pallid streaks of obvious fatty change. There was neither endocarditis nor pericarditis. The liver weighed 1,521 grams, and the Prussian blue reaction in it was not marked. On this account it is possible that the case should not be classed as one of pernicious anæmia, and yet the condition of the blood was typical enough. The spleen was big, weighing 341 grams; it contained two infarcts; it gave no ferrocyanide reaction. The kidneys together weighed 386 grams; they contained old and recent infarcts, but otherwise they were natural, except for anæmic pallor. It is a pity that no mention is made of the iron reaction in them, for in exceptional cases there is a much deeper blue in the kidney cortex than in the liver. The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Zeiss.		Haldane.		Thoma Zeiss.
30 July, 1901	647,619	13	11	0·846	2,857
10 Aug. „	670,000	13	15	1·154	6,850
21 „ „	562,500	11	12	1·091	2,500
18 Sept. „	600,000	12	11	0·916	8,000
4 Oct. „	600,000	12	12	1·000	3,200

Note.—Poikilocytosis was extreme.

The temperature chart was as follows :—
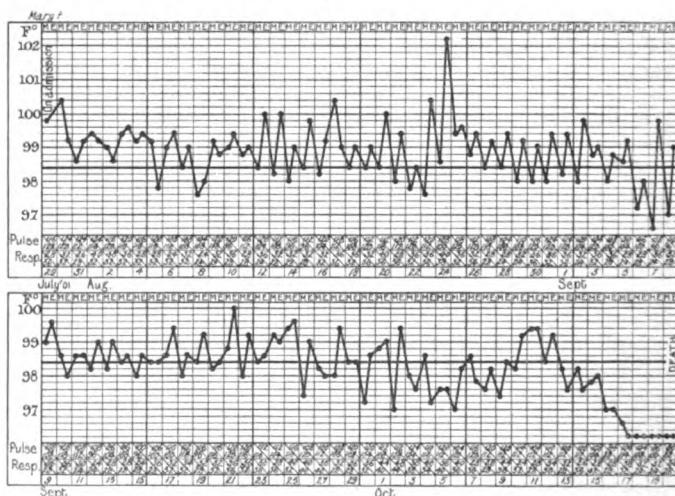
CASE 26.—Ref. No., Vol. 171, No. 80; Post-mortem No. 45, 1901.—
Andrew C., æt. 58, a newspaper correspondent, was admitted under Dr. Pitt
on January 30th, 1901, and died on February 8th, 1901. He came in for
extreme epistaxis, with extensive and large purpuric extravasations and
bleeding from the gums. There were retinal hæmorrhages and extreme
anæmia; lobar pneumonia set in and caused rapid death. He gave the
history that his heart had troubled him greatly for twenty years, during
which time he had had numbers of syncopal attacks. Otherwise he had
been well until hæmorrhages began without apparent cause two months
before admission. At first he only noticed blood in his mouth on waking in
the morning, but later spontaneous epistaxis set in, and it was too severe to
check. He looked pale and bloodless. There was a systolic bruit at the
base; the cardiac impulse was in its normal place. Neither liver nor spleen
could be felt. The nervous system seemed natural. The urine was of
specific gravity 1020, and of dark amber colour; it contained neither blood
nor albumin. Retention of urine occurred, necessitating the use of a
catheter, shortly after which the patient died with a gurgling noise. At the
autopsy the brain exhibited some excess of serous subarachnoid fluid; there
was no intracranial hæmorrhage. There was recent pleurisy on the left
side and a patch of early terminal pneumonia under it. The heart weighed
444 grams., but presented no particular abnormality. The liver weighed
2,030 grams; it was a chocolate-blancmange colour, and gave a very good
Prussian blue reaction. The kidneys together weighed 405 grams; they
were pallid but otherwise healthy; they gave no iron reaction. The spleen
weighed 207 grams. The fact that the patient's temperature rose to 102°
is explainable by reason of the pneumonia. The blood count has not been
completely recorded; the chief proof of pernicious anæmia is therefore the
iron reaction in the liver :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Zeiss.				Thoma Zeiss.
February, 1901	1,925,000	38	?	..	8.125

The temperature chart was as follows :—
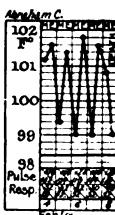
CASE 27.—Ref. No., Vol. 171, No. 107.—Richard C., æt. 44, a tailor, was
admitted under Dr. Pitt on March 12th, 1901, and was discharged relieved
on August 13th, 1901. He came in for great and increasing weakness. In
September, 1899, a year and a half before admission, when he had hitherto
been strong and well, the present trouble began in a manner that seemed
almost sudden. He came over faint when out for a walk, and had to sit
down. He recovered in an hour or so, and paid little heed to the occurrence;
but three months later the same thing happened again; and since then he

had suffered from increasing physical weakness. In August, 1900, he had to lie up in bed for seven weeks. On twenty or thirty occasions there had been epistaxis. Dyspnœa upon any exertion was marked. Appetite remained good, but indigestion was easily produced. There was no œdema, and no other hæmorrhage than epistaxis. There was a decided tendency to diarrhœa. He said he had lost two stone in weight, but he looked well nourished. His pulse rate averaged 92, his respiration rate 22. The teeth were good, but black from smoking. The heart was normal in size, but there were hæmic bruits in all areas. The urine had a specific gravity of 1014 ; it was free from albumin and from blood ; ? indican, ? urobilin. The nervous system was natural except for some decided numbness of the fingers. The retinæ presented no hæmorrhages. Neither liver nor spleen was felt. The patient was treated with arsenic and made one rally, but relapsed whilst still under observation and went out very ill. A friend, writing on August 20th, 1907, says : " Richard Croft died within a month of leaving Guy's. . . . ." The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Zeiss.		? Haldane.		Thoma Zeiss.
12 March, 1901	1,560,000	31	10	0·323	6,000
22 „ „	1,058,333	21	10	0·476	6,000
30 „ „	916,666	18	23	1·278	5,675
4 April, „	1,903,000	38	30	0·789	3,000
13 „ „	1,458,300	29	30	1·035	—
22 „ „	1,634,400	33	30	0·909	4,688
6 May, „	2,566,666	51	30	0·588	6,875
18 „ „	1,874,900	37	33	0·892	7,810
	Went to con	valescent	home for a	short time.	
11 June, „	240,000	5	10	2·000	8,100
20 „ „	900,000	18	10	0·555	8,678
5 July, „	920,000	18	15	0·833	—
15 „ „	1,200,000	24	17	0·708	—
19 „ „	900,000	18	20	1·111	—
24 „ „	850,000	17	15	0·882	—
29 „ „	830,000	17	15	0·882	—
3 August „	860,000	17	15	0·882	—
7 „ „	924,000	18	—	—	—
13 „ „	943,000	19	30	1·579	—

Note.—Films presented many poikilocytes, megalocytes and microcytes. The count of June 11th is possibly in error on the low side ; but even allowing for this it is amongst the very lowest on record.

The temperature chart was as follows :—
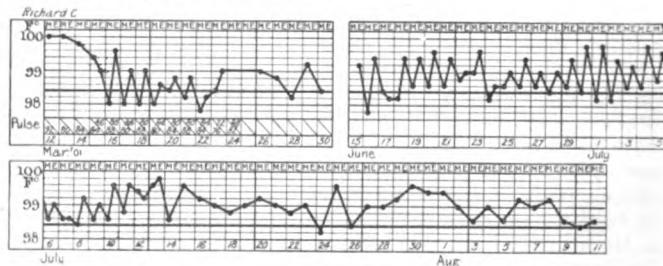
CASE 28.—Ref. Nos., Vol. 171, No. 346; Vol. 173, No. 192; Vol. 178, No. 194; Post-mortem No. 217, 1902.—Charlotte W., æt. 49, a cook, was admitted under Dr. Bryant, on April 4th, 1901, to be discharged slightly relieved on May 10th, 1901. She was re-admitted, under Dr. Pitt, on September 19th, 1901, and re-discharged greatly relieved on October 12th, 1901. She was re-admitted once more on April 2nd, 1902, and died in hospital on May 16th, 1902. She originally came in for vomiting and for being so weak that she could not do her work. She was a widow, and had had no children. Her present trouble began a year before her first admission, and for nine months she was unable to work. She attributed her illness to a sudden attack of diarrhœa and vomiting, which came on abruptly whilst she was lifting a heavy bath. During the twelve months previous to her admission her symptoms had been chiefly gastro-intestinal, together with progressive anæmia and weakness, the various diagnoses suggested being gastric ulcer, gastro-enteritis, and acute on chronic dyspepsia. After her first admission she remained at work for a month, but then gradually relapsed. Her history between the second and third admissions is given below. She was of the pale yellow tint, and "somewhat thin." Her pulse rate averaged 84, her respiration rate 24; the temperature when the patient was most ill was nearly always 100° F. each night. The heart was not enlarged; there were hæmic bruits in all areas. Neither liver nor spleen was felt. There were no retinal hæmorrhages, but there was some degree of optic neuritis, and the fields of vision were concentrically contracted. The urine was not abnormally dark. Vomiting and nausea became prominent symptoms sometimes, partly perhaps as the result of arsenical treatment. Antistreptococcal serum was also used in this case. After her second discharge she continued at work for nearly five months, and then suddenly collapsed after trying to lift a heavy weight. She had to take to her bed at once, and stayed there till her death. She was by now decidedly thinner than at first—indeed, actually wasted. The knee-jerks were very difficult to obtain, and there were shooting pains in the legs and arms, so that very likely the wasting was partly due to peripheral neuritis, and this in turn may have been induced by arsenic. The urine was now rich in urobilin, and occasionally contained a trace of albumin. She died gradually of heart failure. The post-mortem examination revealed the bright primrose yellow colour of the subcutaneous fat, and slight œdema of the legs, arms, and body. The left pleura was generally adherent; the right contained 1200 c.c. of serous exudate; the lungs showed healed phthisis, and they were pale and œdematous, but otherwise normal. The heart weighed 311 grams; the pericardium was healthy, and the valves normal, but the muscle was pale and brownish, and exhibited typical tabby-cat striation. The liver weighed 1512 grams, was of the usual café-au-lait colour, and gave a very marked Prussian blue reaction. Microscopically there were very marked granules in the hepatic cells. The spleen looked

normal microscopically. The kidneys weighed 351 grams together. There is no mention of the Prussian blue test being applied to spleen or kidneys. The blood-counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Zeiss.				
10 April, 1901	650,000	13	26	2·000	7,000
15 May, „	1,800,000	36	41	1·139	5,000
26 „ „	1,800,000	36	40	1·111	7,000
20 Sept., „	1,800,000	36	60 Tollquist	1·666	—
30 „ „	1,600,000	32	42	1·312	-
2 Oct., „	1,512,000	30	33 Haldane	1·100	—
7 „ „	4,250,000	85	36 „	0·423	—
11 „ ,	5,050,000	101	40 „	0·396	—
3 April, 1902	785,714	16	25 „	1·562	6,406
23 „ „	699,000	14	20 „	1·429	9,750
14 May, „	876,000	15	10 „	0·666	4,800

Note.—10th April, 1901, numerous poikilocytes, microcytes, megalocytes, nucleated red cells. 3rd April, 1902, two nucleated red cells seen, many poikilocytes, megalocytes and microcytes. 14th May, 1902, the differential leucocyte count was as follows :—S. 25, L. 3, P. 70, E. 2.

The temperature chart was as follows :—
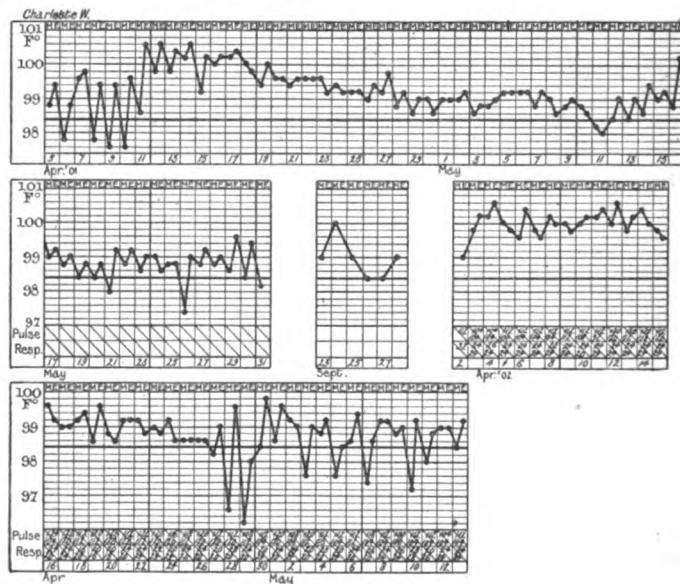
CASE 29.—Ref. No., Vol. 171, No. 132; Post-mortem No. 148, 1901.—
Henry S., æt. 67, a tin solderer, was admitted under Dr. Pitt for constipa-
tion and vomiting on 19th April, 1901, and died on 9th May, 1901.   For at
least three years previously he had been getting paler and more anæmic, and
he had complained of insomnia.   Until then he could cycle well, but since
then he had been too weak to do so.   He had been getting gradually lighter
for two and a half years past.   He had been treated for hypochondriasis.
He had no teeth at all.   Neither liver nor spleen was palpable.   He
suffered from low muttering delirium at nights, getting out of bed continually,
and so forth.   He complained of numbness and tingling in his fingers ; the
knee-jerks were either absent or extremely sluggish, though the pupils reacted
normally.   There were no obvious hæmic bruits.   The urine had a specific
gravity of 1012, and it contained excess of urobilin.   On May 2nd a sudden
mental change occurred, the hands and arms were tossed about in all
directions, and the patient expectorated continually and everywhere ; he
had fits of imbecile laughter also ; bed-sores developed, and in a week coma
and death ensued.   The skin and subcutaneous fat were typically yellow,
but not jaundiced.   The marrow of the femur was dark-red like fresh blood
clot.   The brain exhibited a triangular-shaped effusion of blood in the
right temporo-occipital cortex.   The lungs were the seat of septic broncho-
pneumonia associated with early acute pleurisy.   The heart presented no
pericarditis and no valvular change, but well-marked tabby-cat striation.
The liver was of normal size and colour ; it gave the Prussian blue reaction,
but to a much less degree than do many cases of pernicious anæmia.   The
spleen was of normal size.   The kidneys looked pale, but otherwise natural,
but they gave some degree of Prussian blue reaction.   Microscopically the
marrow of the femur was found to contain normoblasts in abundance.   The
liver cells showed yellow-brown pigment granules within them, especially at
the periphery of the lobules.   A section of one of the muscles of the legs
showed the fibres and their nuclei staining badly, the longitudinal striations
being much less definite than usual.   There was a good deal of pigmentary
deposition in the cardiac muscle fibres, but not much fatty change.   The
stomach exhibited much small-celled infiltration of the submucous coat.
There was only one blood count as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpus- cles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Zeiss.				Thoma Zeiss.
20 April, 1901	1,120,000	22	28	1·273	2,820

No temperature chart is available in this case.

CASE 30.—Ref. Nos., Vol. 169, No. 201; Vol. 181, No. 24, and Vol. 184,
No. 365 ; Post-mortem, No. 238, 1903.—Charlotte R., æt. 46, a housewife,
was admitted under Dr. Taylor on June 5th, 1901, and discharged on August
3rd, 1901.   She came in for " jaundice," which was the lemon yellow colour
typical of pernicious anæmia.   She was a married woman with two children.

She had been a sufferer from " indigestion " frequently, and this had been particularly severe for two months before admission. She had also lost much weight. She looked thin ; her face and body were primrose yellow, but her conjunctivæ were quite white. The teeth were scanty, but those that were left were sound and clean, and there was no stomatitis. There was extensive freckle-like pigmentation of the skin over her abdomen, back, and limbs. The liver, smooth, firm, and uniform, was palpable two inches below the ribs in the right nipple line. The spleen was not felt. The urine varied in specific gravity between 1010 and 1020 ; urobilin was not mentioned. The optic discs and retinæ were natural, and so were the reflexes. The temperature chart was typical. Treatment was by arsenic, and dentures were supplied. The patient was readmitted under the care of Dr. Shaw on November 28th, 1902, and discharged again relieved on January 6th, 1903. A tendency to rheumatoid arthritis had greatly increased meanwhile, and since her last discharge she had not been out of doors, as her knees had been too painful. There was also marked ulnar flexion of the fingers at the meta-carpophalangeal joints, and spindle-shaped swelling of the first inter-phalangeal joints. She also suffered from troublesome " knocking noises " in her head and great dizziness, especially on stooping. She had gradually lost colour again, and had become so weak that she was exhausted by the slightest exertion. There were hæmic bruits in all areas, a bruit de diable in the neck, and slight œdema of the ankles. There had been amenorrhœa since the illness began, though previously the menses had been regular and normal. The urine contained neither blood, albumin, nor urobilin ; it deposited uric acid crystals spontaneously on standing. Again there were no retinal or other hæmorrhages. Greatly relieved by January, 1903, she remained "quite well" for four months, and then she noticed that every-thing she ate tasted sweet, even acid and salt things did so. She became weaker and weaker, her appetite failed, and she became very short of breath. Her bowels were regular. She was re-admitted under Dr. Shaw on June 8th, 1903, and died on June 24th, 1903. The liver was large and smooth as before, the spleen was now palpable, and there were retinal hæmorrhages. The urine again contained no obvious urobilin. The reflexes were natural. Œdema of the legs was considerable, and it increased, extending to the thighs and back, and finally to the arms. The patient became delirious and died comatose. At the post-mortem examination the body was noted to be thin, but not emaciated ; the subcutaneous fat was plentiful and bright yellow, the muscles a dull brown. The bone marrow of the femur was dark red, and microscopically exhibited no fat, but a dense mass of cells, amongst which one could see many erythroblasts of various sizes, large bone-marrow corpuscles, and many white blood corpuscles. The lungs and pleuræ were healthy. The heart weighed 294 grams, was coated by a thick external layer of lemon-yellow fat, had normal valves, and exhibited typical " tabby-cat " striations inside the left ventricle, especially on the musculi papillares. The stomach and intestines looked pallid, but otherwise natural. The liver weighed 1,312 grams ; it was of a pale chocolate colour, and on close inspection it could be seen that the periphery of each lobule was darker and browner than the centre, which was yellower. The organ gave a very marked iron reaction. The pancreas exhibited pigmentary changes. The spleen weighed 130 grams ; it was not tested for iron ; nor were the kidneys, which together

weighed 260 grams, and looked natural except for pallor. The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Leitz.		Haldane.		Thoma Leitz·
11 June, 1901	1,466,666	27	39	1·444	11,428
5 July, „	2,600,000	52	42	0·808	—
18 „ „	3,160,000	63	75	1·190	—
29 Nov., 1902	440,000	9	17	1·888	3,640
2 Dec., „	752,000	15	21	1·400	3,800
8 „ „	1,284,000	26	32	1·230	3,400
10 „ „	1,294,000	26	32	1·230	2,800
21 „ „	2,334,000	47	—	—	4,600
27 „ „	3,296,000	66	58	0·879	4,600
6 Jan., 1903	3,864,000	77	60	0·779	7,032
6 June, „	683,333	14	20	1·429	8,520

Note.—June 11th, 1901 : Many poikilocytes, megalocytes, microcytes, and many nucleated red cells. July 18th, 1901 : Megalocytes numerous. Poikilocytes fewer, no nucleated red cells. November 29th, 1902 : Poikilocytes and megalocytes, and nucleated red cells numerous. Sp. gr. 1027. The differential leucocyte count was as follows :—S. & L. 38, P. 59, E. 1·7, B. 1·3. June 6, 1903 : Typical films

The temperature chart was as follows :—
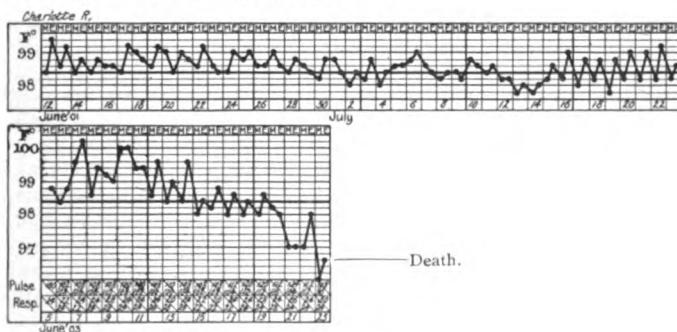
CASE 31.—Ref. No., Vol. 171, No. 382.—James C., æt. 63, a gardener's labourer, was admitted under the care of Dr. Pitt on October 14th, 1907, and was discharged greatly relieved on November 2nd, 1907. He was a widower with eight children. In the spring of 1901 he had what he termed "jaundice," associated with great soreness of his mouth ; the latter was so troublesome that he had been unable to smoke a cigarette for the five months previous to his admission. Besides these more acute symptoms he stated that he had suffered from throbbings in the head and from being weak and generally out of health ever since the loss of his wife in July, 1900. He had not lost bulk ;

his weight on admission was 123 lbs., and it rose to 132 lbs. in a little over a fortnight. He was in the habit of having his bowels moved twice a day regularly. He was a typical lemon-yellow case, the "jaundice" having been in reality the pernicious anæmia colour, and not true jaundice. The temperature tended to be persistently subnormal, thus differing materially from most cases. The pulse rate averaged 74, and the respiration rate 20. The teeth were decayed and in poor condition. The liver was palpable on admission, but not later, and the spleen was not felt. No hæmic bruit was recorded. The urine was straw-coloured and of specific gravity 1012; indican and urobilin are not mentioned; neither albumin nor blood was present. There was no œdema; but before admission there had been a little at times around the ankles. The long bones were decidedly tender. The reflexes were normal. Treatment was by means of arsenic. A former acquaintance reports on August 22nd, 1907, that "James C. went away to the country and has been lost sight of." The rate of recovery of the blood in this case was noteworthy :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Zeiss.		Haldane.		Thoma Zeiss.
22 Oct., 1907 ...	967,500	19	30	1·579	17,000
2 Nov., „ ...	2,350,000	47	45	0·957	—

Note.—Poikilocytes abundant ; no nucleated red cells seen.

No temperature chart is available in this case.

CASE 32.—Ref. No., Vol. 175, No. 168; Post-mortem No. 283, 1902.— Hilda D., æt. 10, a schoolgirl, was admitted under the care of Dr. Taylor on June 27th, 1902, for general weakness, extreme anæmia, and vomiting. She was most gravely ill, and died two days later, on June 29th, 1902. It is quite possible that this case should not be classed as one of pernicious anæmia, for the blood count did not show a high colour index ; and her brother died the same year in Guy's Hospital of an affection diagnosed in his case as " splenic anæmia"; on the other hand, the ferrocyanide reaction in the liver and kidneys at the autopsy suggest pernicious anæmia. At six months of age she had had a very bad illness, of which vomiting and pains in the limbs had been the main symptoms. She recovered completely, but at five years of age she had a precisely similar attack ; and a third when she was six. In each of these last two attacks the illness was diagnosed as splenic anæmia. On June 22nd, 1902, she suffered from a fourth and final attack which began with severe vomiting and with pains all over the body and limbs, especially in the calves of the legs. She was very thin on admission, and extremely anæmic, and of a sallow yellow colour both as to her face and as to her whole body. The spleen could just be felt. The liver was not palpable. There was a blowing systolic hæmic bruit in the mitral, aortic and pulmonary areas. The temperature rose to 101·4°F., the pulse rate to 160, the respiration rate to 60, and the patient died of exhaustion. The post-mortem

examination showed that the skin generally was of a sallow yellow colour, without jaundice; there was very little subcutaneous fat, and no œdema. The lungs and pleuræ were healthy. The heart weighed 147 grams, was covered by lemon yellow fat externally, and exhibited much fatty striation internally, especially in the left ventricle; the valves were normal. The liver weighed 826 grams, was of the " coffee blanc-mange " colour so often seen in pernicious anæmia, and gave a marked ferrocyanide reaction. The spleen weighed 246 grams, it was large, firm, and contained a big red recent infarct. The lymphatic glands seemed to be natural. The kidneys together weighed 104 grams; they were pallid, and gave a marked iron reaction to the ferrocyanide test. The blood count on the day after admission was as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Leitz.		Haldane.		Thoma Leitz
28 June, 1902	1,300,000	26	18	0·692	23,500

Note.—The leucocytes were chiefly polymorphonuclear cells, though neither suppuration nor pneumonia was found post-mortem.

No temperature chart in this case was available.

CASE 33.—Ref. No., Vol. 177, No. 173 : Vol. 182, No. 121; Post-mortem No. 258, 1903.—Alice G., æt. 51, a housewife, was admitted under the care of Dr. Pitt, on March 23rd, 1903, and she died on July 11th, 1903. It is of interest that she was also in hospital in 1902 (June 19th to July 14th), at which time the pernicious anæmia was not obvious, although looking back at it the illness at that time was clearly the same as that from which she ultimately died. In 1902 she was admitted, under her maiden name of Alice Wain, for " general weakness and anæmia," having first complained of an increasing feeling of tiredness in April, 1902. She also noticed that her feet and ankles swelled whenever she was long upon them, and she had a tight feeling across her chest. Four weeks from the first notice of there being anything the matter she began to have troublesome diarrhœa. Her temperature was often 99° F., and on several occasions 99·4° and 99·6°. She was described as " a pale woman with some colour in her cheeks." She was discharged relieved in 1902, and reported that she remained "quite well " from September, 1902, until February, 1903. She then attended as an out-patient for " anæmia and retching," and as she did not improve she was admitted. There were no hæmorrhages, nor had there been any. The patient was a " small, thin, pale woman." Her pulse rate averaged about 90, her respiration rate about 24, and her temperature was usually about 99° F. at night. The liver could be felt one and half inches below the costal margin; the spleen was not palpable; the heart was not obviously enlarged, but it presented loud hæmic bruits both at the impulse and at the base, and there was a venous rumble in both sides of the neck. The urine had a specific gravity of 1020; it was of a full yellow colour, and sometimes it

contained a trace of albumin. There was no obvious urobilin and no excess of indican. Œdema of the legs increased, until finally it extended up into the thighs and back, though there was no ascites. The patient died of exhaustion. At the autopsy the bone marrow of the femur was dark red; the heart weighed 199 grams, and exhibited both tabby-cat striations and petechial hæmorrhages; the liver weighed 1390 grams, and gave an extremely good Prussian blue reaction: the spleen weighed 181 grams; the greater part of the alimentary canal looked perfectly natural, but the sub-mucosa of the last 12 cm. of the ileum and the first 8 cm. of the colon were replaced by a continuous greenish-grey chronic but sloughy ulcer. The walls of the ileum were thickened to something like five times their normal thickness; the ileo-cæcal valve no longer existed as such, and the fibrous contraction of the base of the ulcer had converted the cæcum into a small sacculus, which barely admitted the tip of one's little finger. The vermiform appendix was not involved in the ulceration. Microscopical sections showed the two layers of muscular coat to be quite intact, but the mucosa and submucosa had become entirely replaced by cellular granulation tissue. The cause of this chronic ulcerative ileo-colitis was not obvious; the only definite points were that no evidence of either tubercle or growth could be found. The kidneys were natural except for anæmic pallor. The lungs were healthy. A piece of the liver, and a piece of the liver of another case (acute tuberculous pleurisy with apparently healthy liver in a girl æt. 14), were kindly analysed by Mr. J. H. Ryffel, who reported as follows:—" The normal liver contained 0·14 per cent. of iron; the pernicious anæmia liver contained 0·34 per cent. of iron. Both are measured for the washed dried solid. The results of both are somewhat high, especially for the normal liver, as I found it impossible to wash the pieces of liver used entirely free from hæmoglobin." The blood counts in the case were as follows:—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Leitz.		Haldane.		Thoma Leitz.
19 June, 1902	1,800,000	36	34	0·944	—
29 „ „	1,800,000	36	40	1·111	—
5 July, „	2,500,000	50	40	0·800	4,500
24 March, 1903	1,190,625	24	28	1·166	5,000
12 „ „	1,900,000	38	25	0·658	5,000
23 April, „	1,934,375	39	27	0·692	4,375
28 „ „	1,387,500	28	36	1·285	1,666
11 May, „	1,865,625	37	42	1·135	3,733
19 „ „	2,125,000	42	46	1·095	5,312
28 „ „	2,075,000	41	34	0·829	6,875
2 June, „	2,153,125	43	43	1·000	9,687
9 „ „	1,578,125	32	28	0·875	6,334
16 „ „	1,906,250	38	24	0·631	3,700
22 „ „	775,000	16	22	1·375	6,300
6 July, „	423,000	9	17	1·889	2,000

Note.—March 24th.—Sp. gr. 1035 (chlorof. and benzene), two normoblasts, and 250 leucocytes.   May 1st.—The differential leucocyte count was as follows:—S. 37·5, L. 11·6, P. 49·3, E. 1·6.

The **temperature chart was as follows**:—
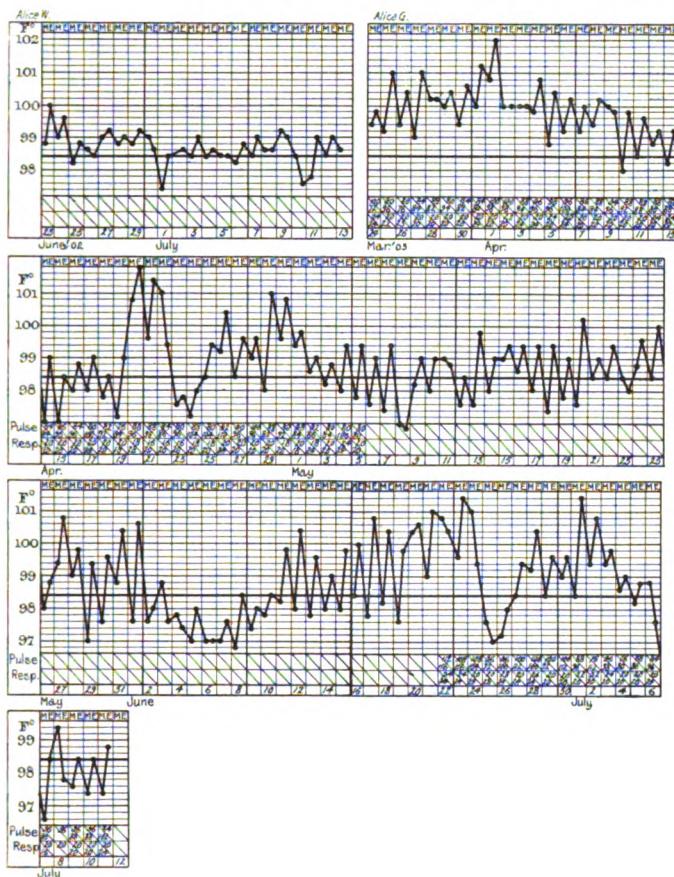
CASE 34.—Ref. No., Vol. 184, No. 632; Vol. 185, No. 260.—Hannah H., æt. 31, a housewife, was admitted under the care of Dr. Hale White on October 1st, 1903, and discharged relieved on December 4th, 1903. She came in for general weakness and for loss of weight of six months' duration, and for vomiting and nausea of three months' duration. For two years past she had been dyspeptic; six months ago, without apparent cause, she began to ail; her menses became scantier each month, and she gradually became weak; she suffered from alternate anorexia and bulimia; headaches and noises in her head came on, and palpitations on the slightest exertion; latterly there had been bleeding per anum, oozing of blood from the gums, and streaks of blood in the vomit. The teeth were much decayed. The face was extremely pallid, and dirty white rather than lemon-yellow. The heart

presented hæmic bruits, and a canter rhythm, though the impulse was in its
natural position. The abdomen was thin enough for the liver to be *seen* one
and a half inches below the ribs. The spleen was just palpable. The urine
contained indican in excess, but no obvious urobilin. Arsenical treatment
was adopted, but it was difficult to maintain on account of severe attacks of
very foul diarrhœa. Various diagnoses were suggested, but that of pernicious
anæmia was finally adopted ; the blood counts were typical. Both knee-jerks
were extremely brisk, and there was ankle clonus in one foot, but not in
the other. The retinæ were natural. The temperature was often 101° F.
each night at first, and as improvement took place it only rose to 100° F.,
and later to less still. After discharge on December 4th, 1903, the patient
remained comparatively well for two months. She then began to go back
again, the menses decreasing as before, weakness and palpitations increasing,
the phlegm becoming streaked with blood, and vomiting taking place after
food. She was re-admitted under Dr. Taylor on June 20th, 1904, and
re-discharged, again relieved, on July 23rd, 1904. She was extremely pallid
on admission, with tenderness of the shafts of the long bones. The liver was
felt two and a half inches below the ribs ; the spleen was not felt ; there was
pyrexia as before ; the lungs were natural ; the heart was of normal size, but
presented hæmic bruits in all areas, and there was a bruit de diable in the
neck. The urine had a specific gravity of 1015 ; it contained no albumin
Arsenical treatment led to troublesome diarrhœa, but at the same time the
patient's general condition greatly improved. An attempt to trace her since
led to a reply from E. Golding, of the same address, on August 15th, 1907 :—
" Mrs. H. has been dead for over twelve months now ;" so apparently she
survived her second rally for nearly two years. The blood counts were as
follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Leitz.		Haldane.		Thoma Leitz.
1 Oct., 1903	987,000	19	29	1·526	5,000
4 „ „	750,000	15	25	1·666	—
7 „ „	650,000	13	25	1·923	—
18 „ „	700,000	14	28	2·000	5,000
25 „ „	900,000	18	28	1·555	—
1 Nov., „	1,100,000	22	39	1·776	—
8 „ „	1,100,000	22	35	1·591	—
14 „ „	1,400,000	28	39	1·393	—
20 „ „	2,500,000	50	60	1·200	—
29 „ „	2,500,000	50	60	1·200	—
22 June, 1904	868,750	17	26	1·529	7.187
8 July, „	2,500,000	50	58	1·160	—

Note.—1st October, 1903: Poikilocytes and megalocytes numerous ; one
nucleated red cell in sixty. 18th October, 1903 : Differential leucocyte count
practically normal. 22nd June, 1904 : S. 54, L. 6, P. 38·5, E. 1·5. Many
megalocytes, poikilocytes and nucleated red cells. 8th July, 1904 : S. 20.
L. 12, P. 60, E. 8.

The temperature chart was as follows :—
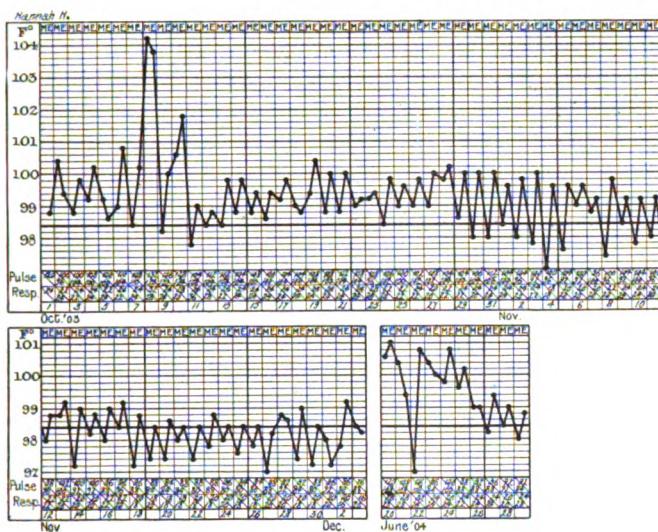
CASE 35.—Ref. No., Vol. 184, No. 631; Vol. 185, No. 180; Post-mortem No. 314, 1904.—James R., æt. 47, a cook and painter, was admitted under Dr. Hale White on October 1st, 1903, and was discharged relieved on October 26th, 1903. He was re-admitted on April 28th, 1904, under Dr. Taylor, and he died on July 3rd, 1904. He had enjoyed very good health, except for an attack of jaundice with dark urine, lasting three months, seventeen years ago, until five months before his first admission. The trouble began with shortness of breath on exertion and some swelling of his ankles when he had been up and about. He had had to take to his bed, and he had been very constipated, so that plumbism was the original diagnosis at home, his occupation being that of a painter. He had lost weight, but not bulk. He had several times tried to return to work, but he had found himself quite unable to go on. He was of a decided lemon-yellow tint of face and body, and he was well-covered with fat. The cardiac impulse was slightly displaced to the left, and there was a systolic bruit audible at the impulse only, but deemed to be hæmic. The urine had a specific gravity of 1020, and a dark reddish colour; urobilin could not be detected in the ordinary way even on several examinations of different specimens, and there was neither blood, albumin, nor bile pigment present. The breath was foul, the tongue furred and tooth-marked, and many of the teeth were decayed. There was no blue line on the gums. Constipation was a considerable trouble. Neither liver nor spleen was felt. The lungs, the nervous system, and the fundi oculorum seemed natural. The pulse rate was from 64 to 72, and the respiration rate from 18 to 24. For two weeks the temperature was almost always 99°F. to 100°F. at night;

later on, as improvement set in, the temperature less often exceeded normal. Arsenical treatment was adopted, and the teeth were attended to radically. The patient was discharged greatly relieved and able to walk about, although the condition of the blood did not seem to be greatly bettered. He remained in "good health" until December, 1903, and then he relapsed. He was re-admitted in a similar condition to that in which he was before, except that he now had very tender bones, was constantly sick, and had developed more œdema of the legs and ascites. The urine had a specific gravity of 1032, and a yellow-brown colour, and it was free from urobilin, bile pigments, albumin, and blood as before. The cardiac impulse was now in its normal place, though, as before, there was a local apical systolic bruit. Neither liver nor spleen could be felt. The peritoneal cavity was incised and drained, the ascitic fluid being clear and free from deposit, not spontaneously coagulable, of a pale greenish yellow colour, and specific gravity 1018. It contained 26 parts of albumin per 1,000. Red and white blood corpuscles were found microscopically, but no pus. The pulse rate averaged 68 to 80, and even at death did not exceed 80 ; the respiration rate averaged 24 ; the temperature was for the most part 99°F. to 100°F. each night, but once rose to 102·8°F. He died of exhaustion ; and at the post-mortem examination it was found that there were fifteen ounces of clear fluid in the left pleural cavity, healed phthisis at the right apex, but otherwise normal lungs. The heart muscle was not unduly pale, and the valves were healthy. There was no pyorrhœa alveolaris. There was general sero-plastic peritonitis without any evidence of tubercles either macroscopically or microscopically. The liver weighed 1,158 grams, and gave a marked Prussian blue reaction. The spleen weighed 105 grams ; it was not tested for iron. The kidneys together weighed 260 grams, and gave nearly as marked a blue reaction as did the liver. Analyses were as follows :—

Analyses for Iron :—

Liver	...	...	1·015 per cent. Fe. in dried tissue.
Spleen	...	...	0·335 ,, ,, ,,
Kidney	...	...	0·512 ,, ,, ,,

<div align="right">J. H. RYFFEL.</div>

The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Leitz.		Haldane.		Thoma Leitz.
1 October, 1903	1,560,000	31	33	1·064	9.100
9 ,, ,,	1,560,000	31	33	1·064	—
16 ,, ,,	1,500,000	30	35	1·166	—
21 ,, ,,	1,800,000	36	36	1·000	—
25 ,, ,,	1,800,000	36	40	1·111	—
30 April, 1904	1,393,750	28	30	1·071	4,687
18 May, ,,	950,000	19	32	1·684	5,625
4 June, ,,	1,520,000	30	32	1·066	6,500

Note.—October 1st, 1903, Poikilocytes and megalocytes, but no nucleated red corpuscles. April 30th, 1904, S. 52·8, L. 4·0, P. 42·8, E. 0·4. 12 nucleated red cells in 500 whites. Many poikilocytes and megalocytes.

The temperature chart was as follows :—
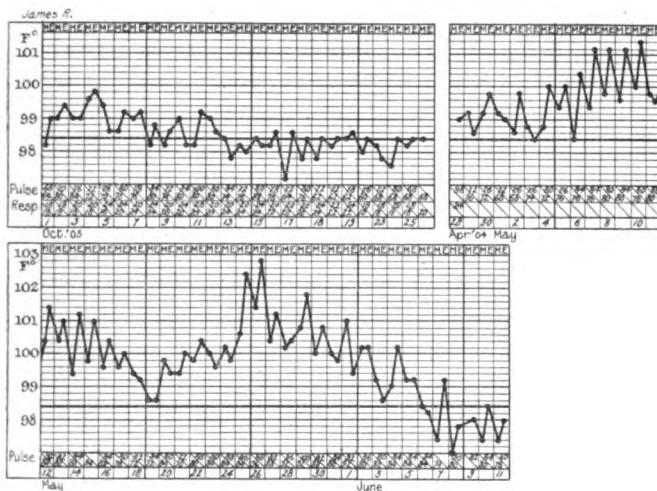
CASE 36.—Ref. No., Vol. 187, No. 19; Vol. 195, No. 162.—Thomas B., æt. 32, an ex-Navy man, was admitted under Sir Cooper Perry on March 16th, 1905, and was discharged much relieved on June 26th, 1905. He gave a long history of illness, and it was very difficult to say at what period the pernicious anæmia originated. In 1889 he entered the Royal Navy as a stoker. In 1892 he contracted syphilis in Alexandria. In 1893 he suffered for three weeks from Malta fever. From 1893 to 1896 he was with the Channel Fleet and in good health, but in 1896 he was invalided from the Navy for varicose veins. Soon after this, in 1896, he began to complain of palpitations, œdema of the ankles, physical weakness, and attacks of severe diarrhœa. He dates his present trouble from this time. In 1899 he was in Canterbury Hospital for these symptoms, and was laid up for sixteen weeks. In 1901 he relapsed, and was again laid up in bed, this time for twenty weeks. In 1903 he had another period in hospital for similar symptoms, but on that occasion he was confined to bed for only two weeks. In 1903–4 he was in Guy's Hospital under Dr. Hale White from December 5th, 1903, to February 11th, 1904, for "anæmia, sclerosis of the cord, electrical treatment," and he was discharged much relieved. There was a hæmic bruit in the pulmonary area, but no enlargement of the heart. There was fairly severe anæmia, but it was constantly of the chlorotic type at this time. A great many blood counts were made, but unfortunately most of them were lost. The temperature chart was typical. There was a special note, "no pyorrhœa alveolaris." The knee-jerks were exaggerated, there was ankle clonus on both sides, together with extensor plantar reflexes. There was no anæsthesia; but three inches above each ankle on the inner side of each leg there was an area of markedly increased sensibility to heat and cold. The pupils reacted normally. He had electrical

treatment, together with arsenic and iron by the mouth, and was discharged
relieved. In 1905 he came under Sir Cooper Perry. The teeth were decayed
and very septic. The tongue was bald and fissured. The pupils were natural;
but as regards the legs there were indications of lateral sclerosis of the spinal
cord as evidenced by ankle clonus on both sides, extensor plantar reflexes,
and increased knee-jerks. The hand grips were good, but the legs were weak
with slight but definite spastic paraplegia. The urine was orange coloured,
of specific gravity 1016; it contained a little albumin and gave an abundant
precipitate of urates. The patient's temperature was nearly always 100° F.
at least once a day. Treatment with arsenic and iron was followed by
considerable relief, and the patient went out relieved. The blood counts
varied more than usual, and the diagnosis of pernicious anæmia could not
be absolutely maintained, perhaps, in the face of all criticism. Nevertheless
the severe anæmia, the high colour index on occasion, if not constantly, and
the course of the disease, suggest that pernicious anæmia is at least possible
if not probable. Dr. F. W. Young, very kindly writing on September 8th,
1907, says: "Thomas B., was admitted to the Faversham Workhouse
Infirmary in June. He was then suffering from profound anæmia. There
was no marked wasting, and I was unable to find anything to account for
his condition except a blood disease. He had a slight cough with expectoration
of watery mucus. There were a few moist sounds in his chest. There was
no enlargement of liver or spleen and no albuminuria. His complexion was
sallow with a hectic patch on each cheek, and he had slight diarrhœa. I put
him on arsenic, but it upset him in even small doses. I am afraid I cannot
tell you anything about the condition of his blood. He is extremely weak
and is mostly confined to his bed. Since his admission he has steadily gone
downhill, and I do not anticipate that he will live many months longer.
I do not think that there is much doubt that the man is suffering from
pernicious anæmia." The blood counts when in hospital were as follows:—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Leitz.		Haldane.		Thoma Leitz.
6 Dec., 1903	3,500,000	70	38	0·543	No leuco-
31　„　　„	3,000,000	60	44	0·733	cytosis.
9 January, 1904	3,400,000	68	44	0·647	10,000
16　„　　„	3,881,250	77	48	0·623	3,437
8 May, 1905	1,660,000	33	28	0·848	1,980
6 June, 1905	1,150,000	23	30	1·304	—

Note.—December 6th, 1903, no nucleated red cells and no obvious
poikilocytosis. January 16, 1904, specific gravity of blood 1042; marked
micro and megalocytosis, and poikilocytosis. No nucleated red cells seen.
S. 48, L. 6, P. 41, E. 5, B. 0, M. 0. May 8th, 1905, S. 47, L. 19, P. 28, E. 4,
M. 2. Eight nucleated red cells seen for 100 whites; poikilocytosis and
megalocytosis very marked. June 6th, 1905, S. 39, L. 7, P. 80, E. 4.

The temperature chart is as follows :—
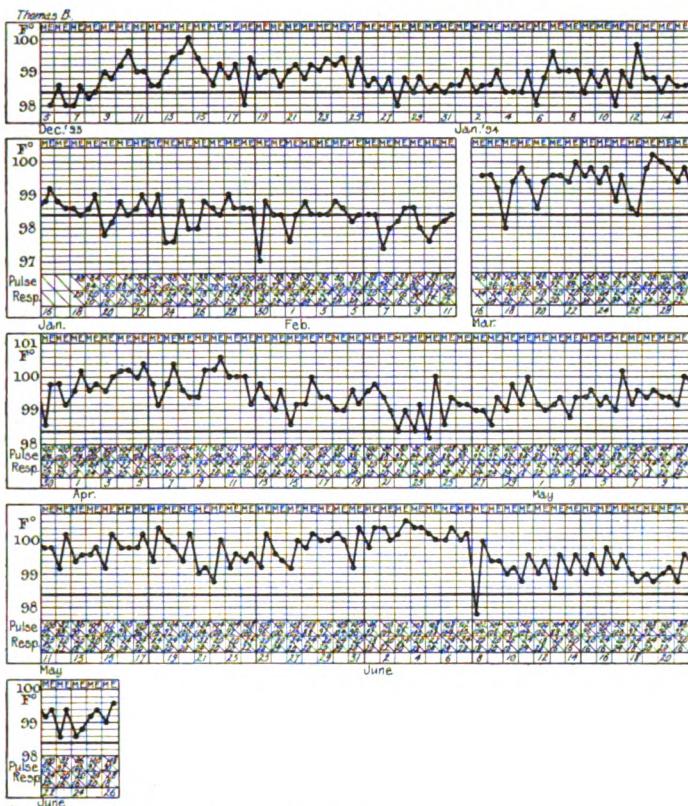
CASE 37.—Ref. No., Vol. 186, No. 35 ; Post-mortem, No. 87, 1904.—
Louisa W., æt. 43, a florist, was admitted into Guy's Hospital under the care
of Dr. Taylor on December 19th, 1903, and died on February 13th, 1904.
She came in for "weakness and vomiting." She stated that she had never
been ill until six months previously, when rapidly increasing weakness
compelled her to give up her work. She also suffered from pains in the
epigastric region and from vomiting, especially after taking food. There
had been a moderate degree of epistaxis on several occasions. The catamenia
had been regular, but latterly the loss of blood had been considerable each
time. The patient was so weak that she could not walk three steps without
resting. At the same time she was not emaciated. The liver was palpable,
smooth, and decidedly tender. The spleen was palpable two and a half
inches below the costal margin. The cardiac impulse was in its normal
position ; there was a loud hæmic bruit in the pulmonary area, but none at
the impulse. The patient's teeth were in particularly good order, and the
mouth was clean. The nervous system appeared to be natural. There were

decided hæmorrhoids, and they bled considerably each day. Indeed, the first diagnosis made in the case was that the anæmia was secondary to hæmorrhage from the piles. The blood counts and the post-mortem findings, however, indicated pernicious anæmia. The pulse rate varied from 88 to 108; the respiration rate from 20 to 32; and the temperature chart showed marked evening pyrexia of over 100° F. The urine had a specific gravity of 1010; on one occasion only did it contain albumin; there was no hæmaturia; uric acid crystals were deposited spontaneously. Arsenical treatment was tried, but there was great difficulty in the case owing to vomiting and diarrhœa, both of which became very severe before death. The latter came about by exhaustion. The chief points noted at the post-mortem examination were: That the lungs were healthy; the heart presented much sub-pericardial fat, with obvious fatty changes in the muscle of both ventricles, particularly the left, especially in the musculi papillares, which were marked with characteristic pallid spots and stripes; the liver was large and pale, and gave an even more marked Prussian blue reaction than usual; the spleen was moderately enlarged, and gave a moderate blue reaction, less in degree than that in the liver; the kidneys were pale, and one of them was scarred from former infarcts; they were not tested for Prussian blue reaction. The blood counts were as follows:—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Leitz.		Haldane.		Thoma Leitz.
20 Dec., 1903	2,050,000	41	35′	0·853	8,000
5 Jan., 1904	1,339,000	27	25	0·926	—
2 Feb. „	787,500	16	24	1·500	6,532

Note.—December 20th, S. 27·2, L. 2·4, P. 66·6, E. 3·8. No nucleated red corpuscles in film. February 2nd, Sp. gr. 1021, by the chloroform and benzene method.

The temperature chart was as follows:—
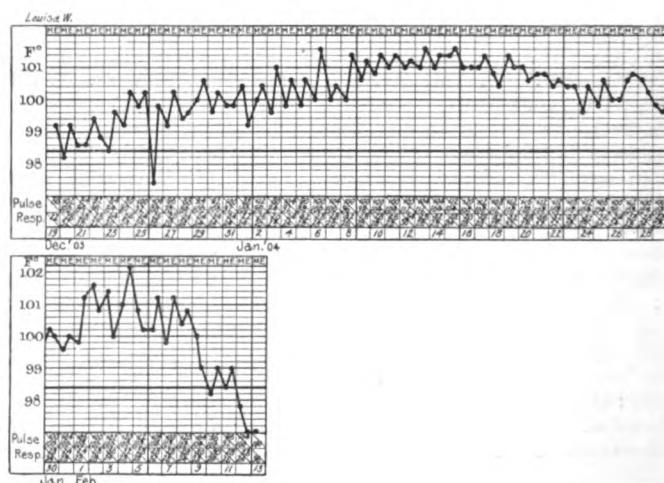
CASE 38.—Ref. Nos., Vol. 186, No. 250, and Vol. 190, No. 334.—Richard P., æt. 48, a joiner, was admitted for general and progressive weakness on May 20th, 1904, and he was discharged relieved on August 16th, 1904. He has not been traced since. He had always lived in England. About two years before his admission he noticed that he was unable to do his work so quickly as usual, and that he was losing power in his hands, arms, and legs. He gradually got so weak that in the end he had to take to his bed. He recovered sufficiently to be able to return to work, only to relapse again in a short while, and be again compelled to stop in bed. Ultimately he noticed that he was getting much paler, and that he was losing in weight, but not in flesh. Lately he had lost control over his defæcation. His bowels had been loose ever since he could remember, and lately, in addition to this, there had been frequent vomiting. His teeth had all been removed years previously. The vomited material contained no blood. The patient also complained considerably of pains in his head and of noises in his ears. On admission he was a very pale yellow colour. The lungs were natural. The heart was not dilated, but there was a well-marked hæmic bruit both in the pulmonary area and at the impulse, and there was a venous hum in the neck. The urine was dark, and had a specific gravity of 1016; urobilin was present, but neither albumin nor blood were found. The knee-jerks were natural. The plantar reflexes were flexor. The only hæmorrhages noted were in the eyes, fair numbers of retinal hæmorrhages being seen. The temperature chart showed a typical rise every night to 99° F., 100° F.. or 101° F. The pulse rate averaged from 104 to 116, and the respiration rate 20 to 24. The patient continued to improve considerably under arsenical treatment, but finally there was a severe relapse whilst treatment was still being continued. Dr. Boycott found that the patient's blood was not hæmolytic to the blood corpuscles of any one of three healthy men. At one time there was much pain in the throat, and the patient also complained sometimes of stiffness of his knee-joints when he moved them. He went out less well than he had been during the middle part of his stay in the hospital, but his subsequent history could not be traced. The blood counts were as follows:—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin. per cent. of normal.	Colour index	Leucocytes per cub. mm.
	Thoma Leitz.		Haldane.		Thoma Leitz.
20 May, 1904	780,000	15·6	18·6	1·154	No leuco-cytosis.
4 June „	3,310,250	60	40	0·666	6,250
7 „ „	2,418,750	48	38	0·800	—
11 „ „	3,336,000	67	68	1·015	6,050
20 July „	3,030,000	61	72	1·180	6,187
29 „ „	3,000,000	60	76	1·266	9,375
12 Aug. „	2,520,000	50	32	0·640	5,312

Note.—May 20th, 1904. Nucleated red corpuscles numerous. Megalo-cytosis not very well marked. Poikilocytosis well marked.

The temperature chart was as follows :—
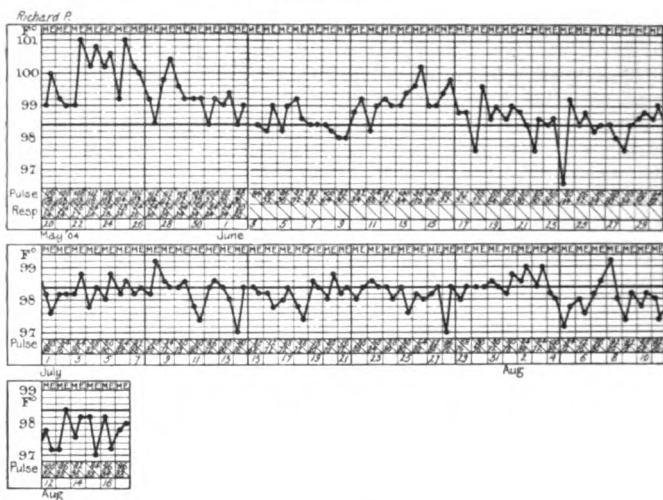
CASE 39.—Ref. Nos., Vol. 170, No. 81 ; Vol. 175, No. 51 ; Post-mortem No. 83, 1902.—Selina K., æt. 41, a married woman, was in hospital under Dr. Hale White, from March 22nd to May 10th, 1901, again from October 7th to December 8th, 1901, and again from February 16th, 1902, to February 21st, 1902, when she died. She was originally admitted for cold shivers, pains over her heart, breathlessness, and vomiting. She had been a strong woman, and had had six children, the youngest of whom was then aged five. She stated that she had been quite well until seven years previous to her admission, when her health began, as she stated, to break up as the result, she thought, of the defective sanitary arrangements of her house. She used often to be sick, and frequently had to stay in bed on account of her weakness. She had been in bed continuously for five months before her admission, and her languidity had been quite bad for over two years before that, during which time there had been constant vomiting after food. She had been attending the Out-patient Department at the hospital for a time, but a year before her first admission she became too weak to continue attending. When seen in bed she was of the typical lemon colour, and she was a very thin woman. Her pulse rate was 72, and her respiration rate 20. Her temperature often reached 100°F. in an evening, sometimes even to 101°F., though it did not always exceed 99°F. The heart was of normal size, but there were hæmic bruits at the impulse, at the base, and over the veins in the neck. The bowels acted regularly. The teeth were in a bad state, but she said this had only been since she had been taking medicine. The urine often contained uric acid crystals in the deposit ; no urobilin was detected on the one occasion on which it was tested for. The nervous system seemed natural. There was nothing abnormal on ophthalmoscopic examination. At one time there were subcutaneous petechiæ. Treatment

was by means of arsenic and by anti-streptococcal serum. Improvement was considerable, and the patient was discharged able to do her housework. Two months later, however, she relapsed, and shortly after that was re-admitted in a very anæmic state. She was again relieved and discharged in December, 1901, and continued well for one month, then gradually became less well, and, finally, acutely worse. On her last admission she exhibited retinal hæmorrhages and severe diarrhœa, the result of ulcerative colitis. Saline infusion was resorted to, but she died in a few days. Shortly before her death she was unconscious and delirious. The lungs were œdematous, but otherwise natural. The heart weighed 336 grams, and its valves were normal. Its cavities were not dilated, but the muscle was pale and exhibited marked tabby-cat striation, especially in the musculi papillares. The liver was of soft consistence, and a pale buff yellow colour, and it gave a very marked iron reaction. The spleen weighed 221 grams. The kidneys weighed 392 grams, and they were large and pale. There was no iron reaction in either kidneys or spleen. The intestines had very thick walls throughout, and on the inner surface of the colon there was a granular and firmly adherent deposit of exudation in small and large patches, the exudate in one place being continuous for 40 centimetres. The condition was one of acute exudative colitis, which had not yet reached the state of ulceration. It was regarded by Dr. Fawcett as secondary and terminal. The bone marrow of the femur was dark red, and microscopically it exhibited many nucleated red cells. The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index	Leucocytes per cub. mm.
	Thoma Leitz.		Haldane.		Thoma Leitz
22 March, 1901	800,000	16	14	0·875	5,000
6 April, "	1,280,000	26	—	—	9,600
7 May, "	4,333,340	86	30	—	14,000
7 October, "	703,000	14	20	1·428	5,200
16 " "	1,050,000	21	15	0·714	6,000
25 " '	1,200,000	24	26	1·083	3,500
9 Nov., "	2,000,000	40	31	0·775	3,800
26 " "	2,500,000	50	50	1·000	2,500

Note.—March 22nd, poikilocytosis and megalocytosis were well marked. Several nucleated red corpuscles were seen in the films. October 7th, poikilocytosis and megalocytosis still well marked, but nucleated red corpuscles no longer seen.

The temperature chart was as follows :—
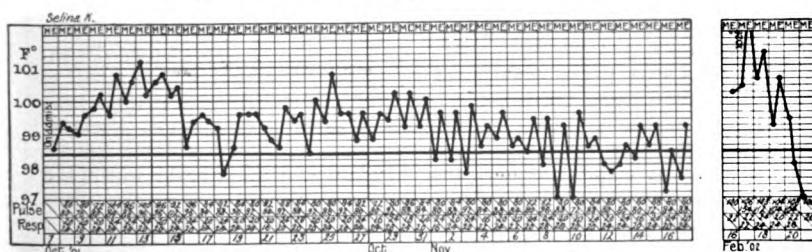
CASE 40.—Ref. No., Vol. 173, No. 600; Post-mortem No. 387, 1901.—
Emily W., æt. 51, a fish-shop keeper, was admitted for weakness, anæmia,
and hæmorrhages under the skin, on October 22nd, 1901, and she died on
October 28th, 1901 She had been subject to severe " bilious attacks and
headache " for eight or ten years, and then, a year before her admission, she
complained of being so short of breath whenever she tried to do anything
requiring exertion. About the same time she began to be weak, and weak-
ness and pallor had progressively increased throughout the year. Three
weeks before admission she had suffered from successive crops of subcutaneous
petechiæ. On admission there was a very extensive purpura all over her
body, but at the same time the lemon-yellow colour of pernicious anæmia
was typical. The pulse rate was 96, and the respiration rate 28. Neither
spleen nor liver could be felt. Epistaxis occurred, and was succeeded by
hæmatemesis, and the patient sank first into an apathy and then a coma,
and died. At the autopsy the liver gave a marked Prussian blue reaction;
the spleen was very small; the heart exhibited both tabby-cat striation
and petechial hæmorrhages, and the stomach and intestines presented a dark
greyish look internally as though from altered blood extravasated in the sub-
mucosa. The blood count was as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpus-cles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index	Leucocytes per cub. mm.
	Thoma Zeiss.		Haldane.		
23 October, 1901	550,000	11	20	1·818	—

Note.—Sp. gr. 1037. Poikilocytosis not marked. No obvious nucleated
red corpuscles in stained films.

The temperature chart was as follows :—
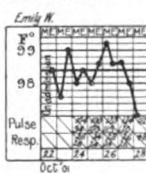
CASE 41.--Ref. No., Vol. 186, No. 145.—Eliza C., æt. 37, a housewife, was
under the care of Dr. Taylor from March 7th, 1904, to April 18th, 1904, and
again from September 13th, 1904, to October 1st, 1904. She came in for
general weakness, anæmia, and loss of weight. At first she weighed
8st. 13lbs., and later rose to 9st. 5lbs. She was a married woman who had
had eight children, and whose husband was alive and well. She had been
born in Poplar, and had always lived in London. Eight years before
admission she had small-pox; in April, 1903, she had an obscure illness,
which was regarded as typhoid fever, but this apparently formed a part of
her present malady, which started in the spring of 1902, at which time she
began to change to the colour she now is, and was so short of breath on
exertion that she could not run upstairs. At the time of her "typhoid
fever," whose main symptoms were diarrhœa and pyrexia, she was in bed
six weeks; her weight just before this had been 13st. In December, 1903,
she was again in bed for three weeks with a similar obscure illness. In the

middle of February, 1904, she suffered from severe diarrhœa continuously for a fortnight, without apparent cause. Throughout the two years previous to her admission she had been repeatedly subject to slight attacks of diarrhœa alternating with constipation, and there had been buzzing noises at the back of her head, fits of retching, occasional epistaxis, and often so much pain over the epigastrium that she was compelled to keep the weight of the bedclothes off that region. She presented the typical lemon-yellow waxy-looking skin. She was well covered with fat all over. The heart was a little dilated, the impulse being in the fifth left intercostal space in the nipple line. There was a hæmic bruit audible in the mitral, aortic, and pulmonary areas, and a bruit de diable in the neck. The spleen could just be felt. The liver was not palpable. The temperature chart was typical; the pulse rate averaged 92 and the respiration rate 24. There were retinal hæmorrhages. The nervous system was natural. The urine was acid, and contained no albumin, blood, sugar, or pus. Arsenical treatment brought speedy improvement, and on April 18th she felt better than she had done for two years. She kept well till June, and then the old symptoms returned. She was re-admitted, and again improved. The temperature was again slightly raised each day. On August 18th, 1907, the husband writes:—" My wife, Eliza C., died on August 9th, 1905." It is noteworthy that the teeth and mouth in this case were in remarkably good order. The blood counts were as follows:—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Leitz.		Haldane.		Thoma Leitz
9 March, 1904	1,112,500	22	33	1·500	7,000
26 „ „	3,850,000	77	51	0·662	8,750
29 „ „	2,590,000	52	47	0·904	—
15 Sept., „	1,500,000	30	50	1·666	—
30 „ „	2,100,000	42	54	1·286	—

Note.—March 9th: To each 100 whites there were 22 normoblasts and 1 megaloblast. Poikilocytes and megalocytes abundant. S. 28, L. 4, P. 68, E. 0. March 22nd: S. 41, L. 9, P. 45, E. 5. For each 100 leucocytes there were 1 normoblast, 3 megaloblasts, 1 gigantoblast, 0 microblast. September 15th: S. and L. 35, P. 64, E. 1.

The temperature chart was as follows:—
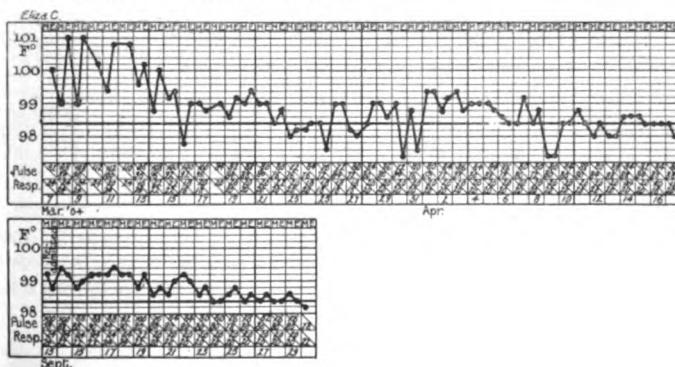
CASE 42.—Ref. No., Vol. 187, No. 402.—Eliza K., æt. 47, a married woman, was in Guy's Hospital from the 27th September, 1904, to the 8th November, 1904, when she was discharged somewhat relieved. Although not much better on her discharge than on her admission, she lived for over a year longer, her daughter writing in August, 1907, as follows:—"My mother, Mrs. K., died in January, 1906. After leaving Guy's Hospital in 1904, she kept fairly well till the following March, when she failed again, and our doctor told us she could not possibly recover; but she rallied again after being in bed for three months, and got fairly well until the following January, when she failed again, and after being in bed only a fortnight she passed away rather suddenly in her sleep: our doctor told me it was from exhaustion, as she had got very weak. Although able to get about between attacks, she was rarely out of the doctor's hands, and never able to do much of her house-work; she was in her 49th year." She was admitted in 1904 complaining chiefly of pains in the epigastric region, and of dyspnœa. She was married and had had seven daughters. She had had anæmia for a long time, and had been under treatment for it for two years, whilst at the same time she was recorded as suffering from enteroptosis. Till May, 1904, she was usually constipated, since when her bowels had shown a tendency to looseness, perhaps as the result of arsenical treatment. In May, 1904, she became particularly short of breath, and though she had not diminished in bulk to a marked degree, she had lost weight. She came into the hospital because she was getting worse. On admission, she did not look particularly wasted, but she was extremely pale and bloodless. There was divarication of the abdominal recti muscles with consequent visible peristalsis. The spleen and both kidneys could be felt, but the liver did not come below the costal margin. The heart was of natural size, but exhibited hæmic bruits. The condition of the optic discs and of the urine is not noted. The temperature chart was typical, going up to 99° or 100° F. each night at first, whilst towards the end of her stay in hospital less rise was noted. Treatment was by means of arsenic. On October 18th, there was a transient attack of herpes labialis. There was nothing in the nervous system to attract particular attention. The blood count was as follows:—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Leitz.		Haldane.		Thoma Leitz.
3 October	1,800,000	36	42	1·166	5,937
4 „	2,350,000	47	48	1·021	5.000
18 „	1,600,000	32	39	1·219	—

Note.—On October 4th, the differential leucocyte count was as follows:—S. 53 per cent., L. 2 per cent., B. 45 per cent., E. 0 per cent. In films two large nucleated red corpuscles were seen in counting each 100 leucocytes.

The temperature chart was as follows :—
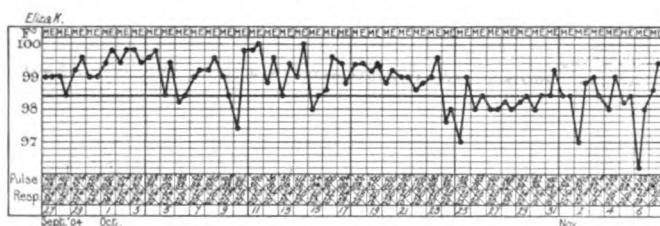
CASE 43.—Ref. Nos., Vol. 187, No. 319 ; Vol. 193, No. 491; Vol. 195, No. 72 ; Vol. 205, No. 225.—Frederick V., æt. 22, a shoemaker, first came under the care of Dr. Hale White from August 2nd to December 15th, 1904. There was a long and indefinite history of increasing weakness and unfitness for work, and upon examination the chief thing that attracted attention was the colour of the skin. The man was not emaciated, though tall and spare. The lips were pale, but the skin of the face, instead of being primrose or lemon yellow, had an unhealthy sallow tint, and upon closer inspection it became clear that there was an abnormal pigmentation both of the face and all over the limbs and trunk, partly in small dark-brown freckle-like spots, and partly in more diffuse brown areas. Addison's disease at once suggested itself as a diagnosis, and at first sight this seemed to be confirmed by the presence of well-marked pigmented streaks and spots within the mouth, particularly on the inner aspect of the cheeks, precisely like that which occurs in Addison's disease. The difficulty in diagnosis was rendered greater by the variation in the colour index of the blood, which was sometimes low and sometimes high. Dr. Hale White laid much more stress upon the high colour indices than upon the low ones, and his diagnosis of pernicious anæmia was confirmed by post-mortem examination in 1907, when the Prussian blue reaction in the liver was typical, and the supra-renal capsules were natural. The heart was of normal size, but there were well-marked hæmic bruits at the impulse and in the aortic and pulmonary areas. Neither liver nor spleen could be felt. The urine had a specific gravity of 1012, was acid in reaction, contained neither albumin nor blood, and only occasionally gave a urobilin band. There was evidence in this patient of degeneration in the spinal cord, for the plantar reflex on each side was persistently extensor, and there was a peculiarity in the man's sensations in the legs, in that whereas he could feel well enough to distinguish heat from cold, and pain from touch, he was insensible to the sensations usually caused by strong electrical shocks over considerable areas both above and below the knees. On many occasions there was blood in the motions, but no other hæmorrhage. The ophthalmoscopic examination showed no retinal changes. Towards the end acute pleurisy developed and the patient was a good deal troubled with œdema of his legs. The pulse rate varied from 80 to 100, the respiration rate from 18 to 24, and the temperature chart was not so typical as some, though it rose more or less in the evening, upon a good many occasions to between 99° F. and 100° F. Treatment was by means of arsenic for the most part, in addition to which on various occasions suprarenal extract, iron, and bone

marrow were administered. He rallied to a certain extent in 1904, but was again in the hospital in 1905, both under Dr. Hale White and under Sir Cooper Perry. Though his improvement was not objectively great, he survived till 1907, dying in an infirmary on March 21st, 1907. The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Leitz.		Haldane.		
5 Aug., 1904	2,100,000	42	44	1·047	2,400
24 „ „	2,625,000	52	36	0·692	—
3 Sept.. „	2,260,000	45	36	0·800	—
6 „ „	2,470,000	49	34	0·694	3,125
3 Oct., „	1,450,000	29	37	1·276	2,656
14 „ „	2,060,000	41	34	0·829	2,188
20 „ „	1,350,000	27	34	1·259	2,810
28 „ „	1,760,000	35	35	1·000	2,030
12 Nov., „	1,650,000	33	36	1·091	1,800
20 „ „	1,650,000	33	36	1·091	2,500
1 Dec., „	1,650,000	33	36	1·091	1,500
10 „ „	2,200,000	44	37	0·841	2,000
20 Jan., 1905	1,731,250	35	36	1·029	—
3 Feb., „	1,350,000	27	27	1·000	1,250
2 Dec., „	1,750,000	35	45	1·286	1,800
14 „ „	1,750,000	35	26	0·743	4,375
3 Aug., 1906	2,150,000	43	44	1·023	6,850
24 „ „	2,100,000	42	44	1·047	6,700
10 Sept., „	2,280,000	46	46	1·000	5,000
17 Oct., „	950,000	19	22	1·158	3,400
9 Nov., „	2,533,333	51	—	—	7,812
16 „ „	2,333,333	47	30	0·638	7,500
29 Jan., 1907	2,500,000	50	—	—	5,600

Note.—On February 3rd, 1905, seven nucleated red cells seen in counting 100 white cells. The differential leucocyte count was as follows : S. 68 per cent., L. 2 per cent., P. 27 per cent., E. 3 per cent. August 3rd, 1906 : Films showed poikilocytes, microcytes and megalocytes, and one or two normoblasts. Numbness in the legs now very marked. September 10th : Poikilocytosis well marked ; no nucleated red cells seen. November 9th : The patient was taken to the strong room, not so much for delirium as for general violence and foulness of language. November 16th : Pleurisy developed in left side. November 27th : Aspiration of chest was performed. August 5th, 1904 : Poikilocytes well marked ; necrobiosis of red cells ; megalocytes very numerous ; no nucleated red corpuscles ; no retinal hæmorrhages. August 24th : Films again showed great numbers of microcytes, megalocytes and poikilocytes ; no nucleated red corpuscles. September 3rd : Nucleated red corpuscles present in films to-day. September 6th : Films as before ; differential leucocyte count as follows : S. 58, L. 4, P. 33, E. 5 ; in counting 500 white corpuscles, 5 normoblasts, and 2 megaloblasts were seen. September 13th : S. 49, L. 3, P. 46, E. 2 ; it was noted on this day that the teeth were in particularly good condition. October 3rd : S. 62, L. 2, P. 32, E. 4 ; in counting 400 leucocytes, 6 normoblasts, 38 megaloblasts, and 1 gigantoblast
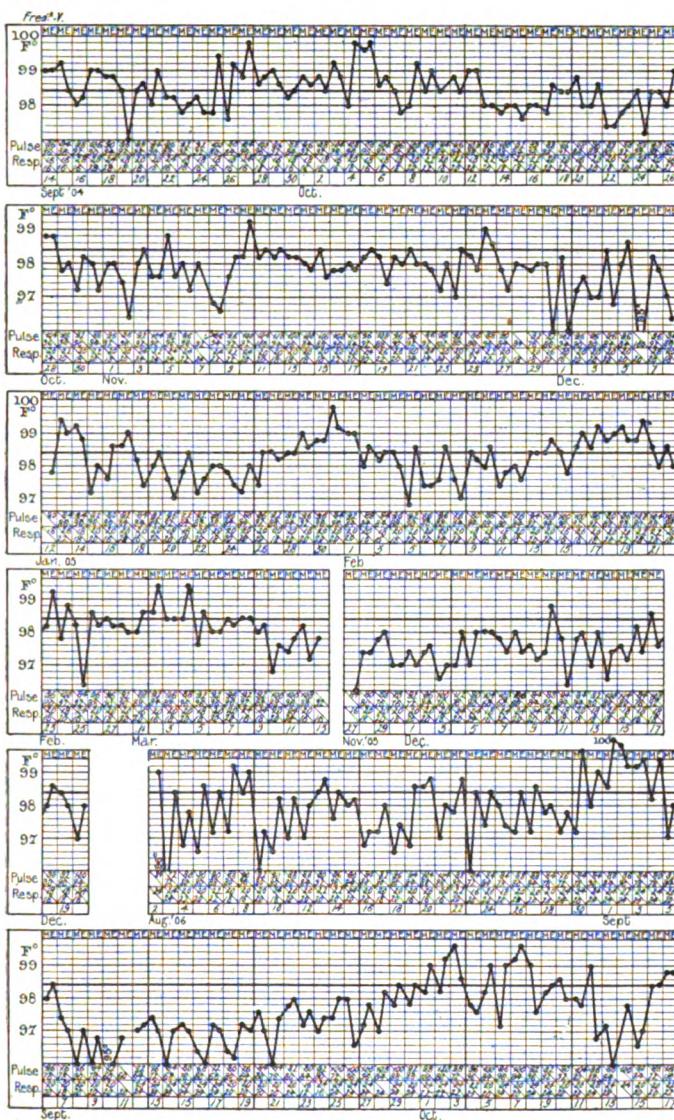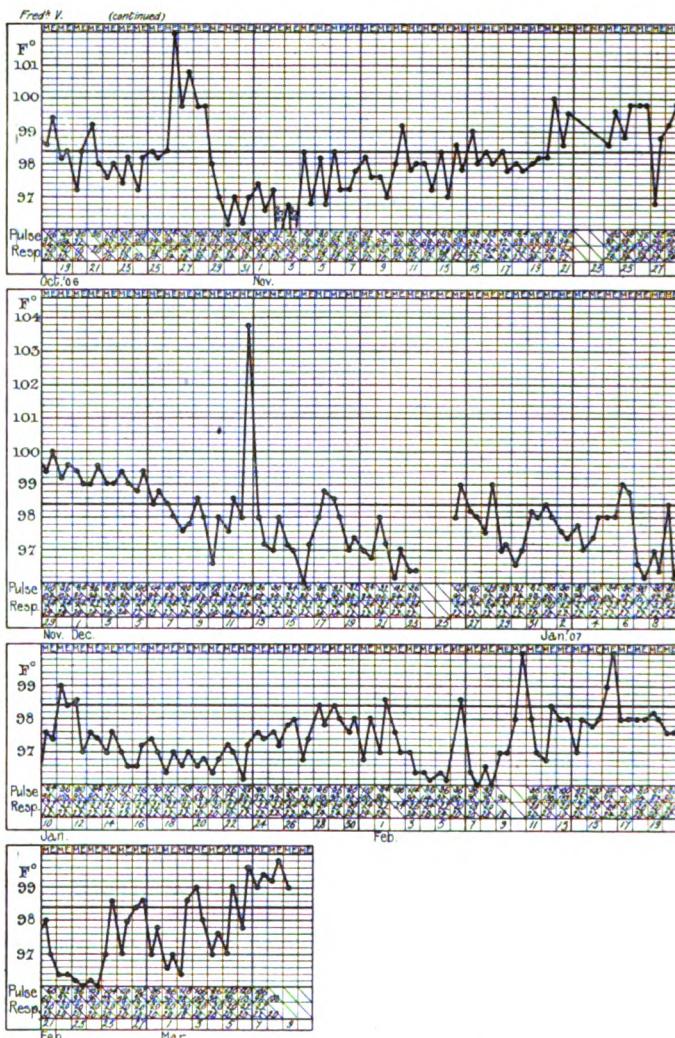
were seen ; punctate basophilia was very marked. October 14th : Films showed
many poikilocytes, punctate basophilia less marked ; megalocytes were very
numerous, however, and nucleated red cells seen ; differential leucocyte count
as follows : S. and L. 68, P. 27, E. 5 ; three megaloblasts were seen while
counting 200 leucocytes. October 20th : Differential leucocyte count as
follows : S. 73, L. 2, P. 23, E. 2 ; five megalocytes and two megaloblasts
seen while counting 200 leucocytes. Urobilin in the urine was estimated
on the 20th, October at 0·008 g. and 0·10 g. on the 21st. October 28th :
Differential leucocyte count as follows : S. and L. 58, P. 38, E. 4 ; poikilocytes

still marked, but no nucleated red cells seen, and no punctate basophilia. November 12th : Films as before, differential leucocyte count as follows : S. 70, L. 1, P. 25, E. 4. November 20th : Differential leucocyte count as follows : S. 67, L. 0, P. 31, E. 2 ; no nucleated red cells seen ; sodium cinnamate was now given to see if leucocytosis could be produced ; treatment for some time past had been by red bone marrow, which had been no good at all. November 21st : Ten grains of sodium cinnamate given hypodermically. November 22nd : Ten grains more. December 1st : Films were similar to what they had been before, and no nucleated red corpuscles present ; collargol given intravenously ; leucocytes did not increase. December 10th : Urobilin : total amount December 1st : 0·076 grains. December 4th : 0·176. December 8th : 0·140.

For temperature charts, see pages 175 and 176.

CASE 44.—Ref. No., Vol. 188, No. 45.—Charles W., æt. 65, a foreman in a coal-tar products factory. Admitted under Dr. Pitt on November 10th, 1903, and discharged relieved on February 24th, 1904. His main symptoms were weakness and shortness of breath. He stated that his health had been perfectly good until October 2nd, 1902, on which day he fell ill of a malady which was diagnosed as bronchitis and pleurisy at the time ; since then he had never been well, though he had tried to keep on at his work. The shortness of wind had been particularly marked for six months previous to admission, and for eight months he had been greatly troubled by numbness in both hands and both feet. After being about there would be œdema of the ankles, but there was none when he stopped in bed. Vomiting, especially after food, had been frequent during the last few months. The bowels had been constipated. Three weeks before admission there had been a little blood with the motions and after them, attributed to piles. The chief points of the case were : The typical yellow colour, tenderness of the bones of the legs, a pulse rate varying from 86 to 100, a temperature chart which often reached 99° F., but seldom exceeded it ; a liver which was just palpable, though the spleen was not ; hæmic bruits both at the impulse and at the base of the heart ; a normal position of cardiac impulse ; considerable purpura upon the legs at one time ; normal knee-jerks and other reflexes. Good clean teeth and mouth. Urine dark orange, of specific gravity 1014, and free from albumin and blood. Weight of patient 9st. 10lbs., rising to 10st. 2lbs. Other points, such as optic discs and retinæ, urobilinuria, etc., are not mentioned. The patient went out relieved, but it was ascertained that he soon relapsed, and died on December 7th, 1904. The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Leitz.		Haldane.		Thoma Leitz.
12 Nov., 1903	2,133,000	43	45	1·047	5,625
24 „ „	1,968,700	39	36	0·923	—
12 Dec., „	2,475,000	49	50	1·020	5,937
13 Jan., 1904	2,583,333	52	50	0·961	7,500
17 Feb., „	2,950,000	59	57	0·966	11,875

Note.—November 12th, specific gravity of blood 1040 (chloroform and benzene). S. 51·6, L. 0·8, P. 39·6, E. 8·0. Poikilocytes and megalocytes plentiful. Eight normoblasts and 1 megaloblast to each 250 leucocytes.

The temperature chart was as follows :—
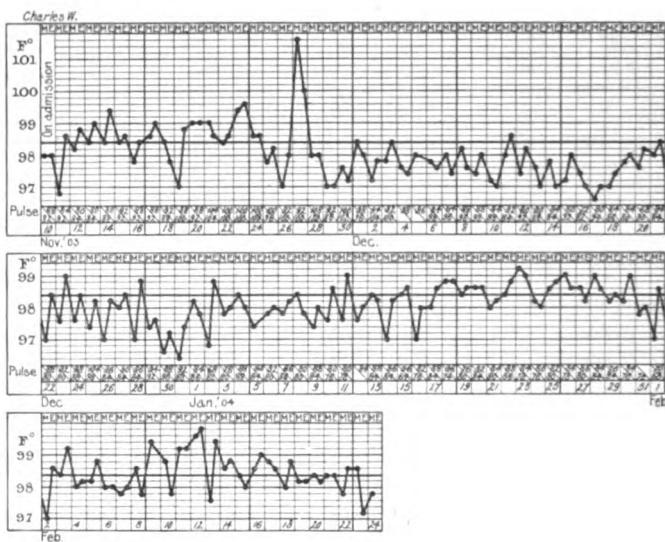
CASE 45.—Ref. No., Vol. 192, No. 56.—Fanny B., æt. 39, spinster, was admitted under Dr. Taylor on December 5th, 1904, and was discharged greatly relieved on January 23rd, 1905. She came in for weakness and loss of appetite. She was born in Dublin, and had had diphtheria at nine years of age, since when she had had exuberant good health until 1903, when her left leg was amputated above the knee for gangrene of the foot, due to arteritis and thrombosis, the cause of which at so early an age was not obvious. She remained quite well after the operation, getting about on crutches, until September, 1904. She then developed a very septic sore throat and extreme diarrhœa that lasted a week, attributed to a bad smell from drains. After this she remained very weak, and every little thing made her vomit. She had the typical lemon-yellow skin, and later developed the salmon-pink flush over the cheeks which is frequent in cases recovering from pernicious anæmia. She was decidedly plump, and although so anæmic she was still vivacious when resting in bed, though she was too weak to walk across the room. There were no retinal nor other hæmorrhages. The heart was of natural size, and there was a systolic bruit in the pulmonary area and a bruit de diable in the neck. Neither liver nor spleen was palpable. The urine had a specific gravity of 1018 ; it contained neither albumin nor blood nor pus, no bile salts and no urobilin to the spectroscope test. The reflexes were natural. Pulse rate and respiration rate were somewhat above normal, and the temperature was often 99°F. to 100°F. at night. Arsenical treatment led to a remarkable degree of recuperation ; but attempts to trace the patient

since she left the hospital have failed.   The blood counts were as follows:—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Leitz.		Haldane.		Thoma Leitz.
6 Dec., 1904	1,000,000	20	35	1·750	6,875
14 „ „	1,462,500	29	48	1·655	No leuco-cytosis.
4 Jan., 1905	4,300,000	86	68	0·791	7,812
11 „ „	3,600,000	72	60	0·833	—
19 „ „	5,600,000	112	98	0·875	---

Note.—6th December, 1904 : S. 31, L. 14, P. 52, E. 3 ; many poikilocytes and megalocytes, and 16 nucleated red cells (normoblasts or megaloblasts) to every 100 white cells = 1,100 per cub. mm.   14th : S. 33, L. 14, P. 50, E. 3 ; 5 nucleated red cells to 100 whites.

No temperature chart is available in this case.

————

CASE 46.—Ref. No., Vol. 195, No. 59.—Annie P., æt. 50, a stewardess on a boat, was admitted on January 11th, 1905, and was discharged very slightly relieved on 20th February, 1905.   She died soon after (see below).   She gave a history of gradually increasing debility, with vomiting, diarrhœa, and indigestion extending over four years, and dating from an attack of "enteric fever" contracted at Naples.   During the four years there had been many rallies, alternating with exacerbations in the symptoms that kept the patient in bed for weeks at a time.   There was considerable pyorrhœa alveolaris, also slight œdema of the ankles, and a purpuric eruption.   The heart was dilated, so that the impulse was in fifth left inter-costal space one inch outside the nipple.   There were hæmic bruits in all areas.   The spleen was felt coming an inch below the ribs.   The liver could not be palpated.   Vomiting and diarrhœa were troublesome symptoms, but it was hardly possible to exclude arsenic as their cause, unless the original "typhoid fever" was in reality diarrhœa at the beginning of pernicious anæmia.   On inquiry it turned out that she was only in bed four days for it, so that the enterica seemed unlikely.   The pulse rate averaged 80 to 104, the respiration rate 20 to 28, and the temperature was up to 99° F. or 100° F. each night.   Though a married woman, she had had neither child nor miscarriage, and menstruation had ceased three years before she came into hospital.   She was a well-nourished woman of the lemon-yellow tint.   She stated that at one time she had had so much pigmentation of the skin that her own doctor had diagnosed Addison's disease, but there was no such extensive pigmentation to be noted now.   The nervous reflexes were natural, but subjective sensations of great numbness in her fingers and toes were complained of, especially in cold weather, and the patient was also troubled by the fact that she could not put her hands into cold water without the fingers going dead.   The pyorrhœa alveolaris was treated by Mr. Maggs, and arsenic was given.   Notwithstanding the use of this drug, the diarrhœa and vomiting both lessened, and the patient herself felt much better, though her blood counts did not improve much.   The cardiac impulse came into the

nipple line. The husband gave the following history on 29th August, 1907 :—
"After leaving Guy's, my wife went to a convalescent home, which she left very weak and ill. She rallied slightly when at home, being some days comparatively well, others ill and depressed. She had a very bad colour, coppery shade. She suddenly lost consciousness, and finally died on the 1st April, 1905." The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Leitz.		Haldane.		Thoma Leitz
11 Jan., 1905	1,856,000	37	55	1·487	4,200
7 Feb., „	2,040,000	41	50	1·220	—
22 „ „	2,020,000	40	55	1·375	4,000

Note.—January 11th: S. 40, L. 6·4, P. 53, E. 0·6.   February 22nd : S. 35, L. 4·4, P. 60, E. 0·6.

The temperature chart was as follows :—
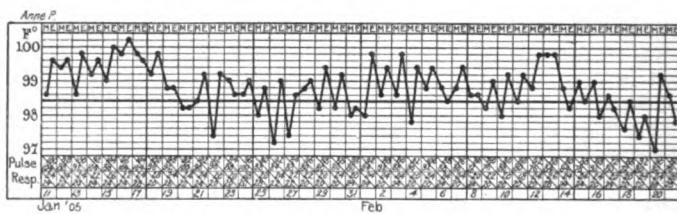
CASE 47.—Ref. No., Vol. 192, No. 82.—John K., æt. 55, a groom and gardener, was under the care of Dr. Taylor from February 3rd, 1905, to April 14th, 1905. He came in for giddiness and weakness, and marked numbness in hands and feet. He had always led a healthy outdoor life, and drank two pints of beer a day regularly. He gave only a history of three weeks' illness, beginning with an attack of severe vomiting ; and he had been in bed for two weeks previous to his admission to hospital. His weight was 11st. 11lbs., and he did not look wasted. There was slight œdema of the ankles, a bruit de diable in the neck, and a hæmic bruit at the cardiac impulse, the heart sounds being barely audible elsewhere. Although his severe illness was only of three weeks' duration, he stated that for over twelve months past he had had a feeling of numbness and tingling in his hands and feet, which had been getting worse, especially in cool weather. Latterly he had been subject to attacks of sweating, giddiness, and blurred vision when at work, so that he has several times had to clutch hold of something to prevent himself from falling. He had had no actual "fits." Three weeks ago, when feeding the calves before breakfast, he was suddenly seized with vomiting, and once since then he has had a sudden attack of nausea during which he tried to vomit, but could not. He was a strongly-built man, but very pale and yellow, and too weak to walk up the ward. When questioned, he stated that he had himself noticed the yellow pallor coming and going for

more than six months past. The exertion of getting to the ward was followed by six separate attacks of vomiting in rapid succession. The knee-jerks were increased in his knees, but there was no ankle clonus and the plantar reflexes were flexor. The teeth were few, but those that were left were clean and healthy. The urine was very dark brandy colour, acid, and of specific gravity 1026. No blood nor albumin present, nor bile pigment. The temperature was frequently 100° till the last two weeks of his stay in hospital when it was nearly normal. Neither liver nor spleen was palpable. C. A. K., of the same address, writes on August 20th, 1907 : " In answer to your letter, my husband remained much the same until the cold weather came. From September last until April, 1907, he was very ill indeed ; no one ever thought he could possibly recover. We consulted another doctor who recommended him extract of malt and cod liver oil ; since then he is much better, able to get about and do light work." A further report from Dr. Sydney Moberly, of Winslow, Bucks, records the fact that John Kimble survived in a wonderful way, but died on April 21st, 1908. The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Leitz.		Haldane.		Thoma Leitz.
7 Feb., 1905	1,550,000	31	35	1·129	—
23 „ „	1,025,000	20	38	1·900	—
2 Mar., „	1,370,000	27	—	—	—
13 „ „	1,900,000	38	33	0·869	7,500
20 „ „	1,550,000	31	43	1·387	—
31 „ „	1,950,000	39	44	1·128	—
10 April, „	2,062,500	41	40	0·976	—
14 „ „	2,750,000	55	45	0·818	—

Note.—7th February, 1905 : S. 20, L. 9, P. 66, E. 5, B. 0 ; many poikilocytes, megalocytes and nucleated red cells. 2nd March 1905 : S. 23, L. 6, P. 67, E. 4, B. 0.

The temperature chart was as follows :—
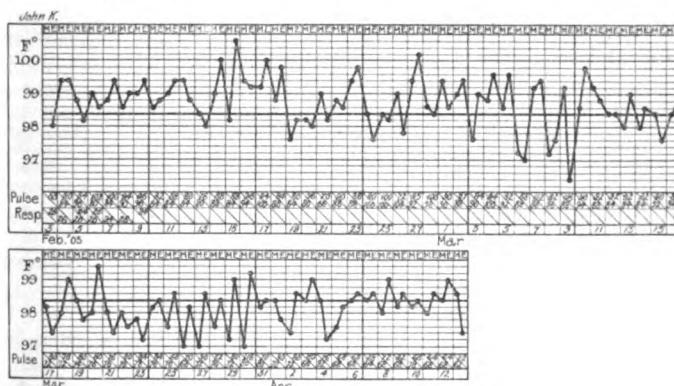
CASE 48.—Ref. No., Vol. 195, No. 662 ; Post-mortem No. 539, 1905.—
Frederick M., æt. 45, a bootmaker, was admitted for extreme weakness,
under the care of Sir Cooper Perry, on October 24th, 1905, and he died
on November 29th, 1905.   In August, 1904, he noticed that he gradually
began to get very yellow, without anything very definite being the
matter.   He had no pain, and he continued to work, though he got
progressively weaker and weaker.   He and his friends thought his yellowness
was "jaundice."   Latterly he had become extremely nervous and irritable,
and for a year past he had had diarrhœa on and off.   By the time of his
admission he became light-headed and suffered from delusions ; for example,
he insisted that there was a bowl of flowers on the table when there was
none.   His temperature chart was typical, seldom coming below 98·4° F.,
and usually reaching to 100° F. or 101° F. each evening.   The highest tem-
perature was 103·2° F.   The pulse rate varied from 92 to 120, the respirations
from 18 to 24.   The man was well nourished, but extremely pale and weak.
The skin generally was of the lemon-yellow tint, whilst the sclerotics were
pearly white.   There was a tendency to pigmentation in the form of
scattered pale brown spots on the trunk.   By this time, however, he had
been having arsenic for a long while, both at St. Bartholomew's Hospital
and in the Guy's Hospital Out-patient Department, pernicious anæmia
having been diagnosed in August, 1904.   On his admission the heart was of
natural size ; there were hæmic bruits in all areas.   The urine had a specific
gravity of 1015 ; it was clear, pale yellow, and no indican nor any urobilin
could be detected in it in the ordinary way.   The knee-jerks and plantar
reflexes were natural, nothing in the nervous system appearing to be
abnormal except for the delusions mentioned.   The latter may have been
due to the many retinal hæmorrhages that, together with the definite
exudation around the optic discs, were confirmed by Dr. Eason.   The mouth
was in a dirty state and the teeth bad.   Neither liver nor spleen was felt.
The patient sank gradually, and during the last twenty-four hours the
breathing became very shallow, without being very fast.   The lungs became
"full of loud moist sounds," and death ensued.   All the viscera were
noticeably pale.   The lungs were œdematous.   The heart weighed 487 grams,
and exhibited well-marked tabby-cat striation in both ventricles.   The liver
gave a marked Prussian blue reaction.   The spleen weighed 306 grams.   The
kidneys gave as marked a Prussian blue reaction as the liver, and they
weighed 481 grams.   The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpus-cles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Leitz.		Haldane.		
24 October, 1905	905,000	18	20	1·111	—
1 Nov., „	1,105,000	22	30	1·364	—
5 „ „	910,000	18	25	1·388	leucopenia

Note.—Poikilocytosis marked ; several nucleated cells seen, some with
karyokinetic figures ; many megalocytes.

The temperature chart was as follows :—
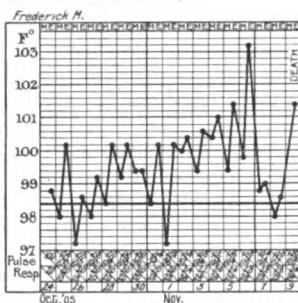
CASE 49.—Ref. No., Vol. 198, No. 79.—Sarah B., æt. 41, was in the hospital, under the care of Dr. Taylor, from November 15th, 1905, to March 7th, 1906. She was a schoolmistress by occupation, and had lived in Norfolk all her life. She was married, and had had no children, although there had been two miscarriages. Her present trouble dated to four years before her admission, when she developed continuous diarrhœa together with breathlessness. Then her fingers began to tingle, and this tingling soon spread to the whole of her body and legs. In April, 1905, her left leg became very weak and shaky, and some little time later her right leg followed suit. In July, 1905, the patient was so weak that she took to her bed, and had been there ever since. She had noises in her head, which were very troublesome. She was of a typical lemon-yellow tint with many brown spots upon her body and limbs. She had no teeth of her own, but a good set of false ones. The urine had a specific gravity of 1015 ; it was acid, and contained no obvious abnormality, excepting that upon careful search a small quantity of urobilin was detected. Her lungs were natural. There is no mention of liver, spleen or optic discs. As regards the nervous system, the wrist-jerks, elbow-jerks, and knee-jerks were all greatly exaggerated. There was an extensor plantar reflex on both sides with ankle clonus and some spasticity of the legs. The only hæmorrhage from which she had suffered was a sudden profuse hæmatemesis when she was out walking nine years before her admission. There had been no recurrence of this. The temperature was slightly but typically raised in the evening. Her apparent anæmia was greater than that usually measured by the blood examination. After her relief and discharge from Guy's Hospital she remained well at home for a short time, and then relapsed in November, 1906, becoming bedridden with much the same symptoms and physical signs as before, with the general appearance of one who was *in extremis* from hæmorrhage. The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Leitz.		Haldane.		Thoma Leitz
15 Nov., 1905	3,100,000	62	75	1·209	—
10 Dec., „	4,500,000	90	80	0·888	—
12 January, 1906	5,600,000	112	100	0·892	—

Note.—November 15th, 1905 : Blood films showed marked poikilocytosis, but no nucleated red cells. The differential leucocyte count was as

follows: S. 20, L. 9, P. 67, E. 4. January 12th, 1906: The differential leucocyte count was as follows: S. 34, L. 1·5, P. 62, E. 1, B. 1·5.

The temperature chart was as follows :—
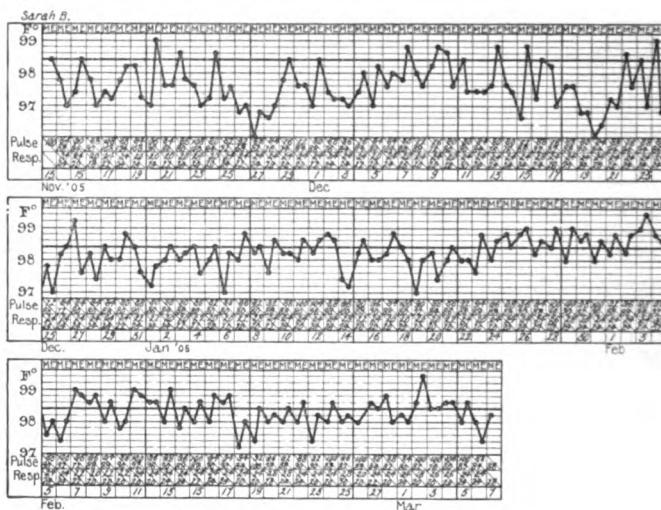
CASE 50.—Ref. No., Vol. 19?, No. 412.—Gideon P., æt. 31, a bricklayer, was admitted under Dr. Hale White on October 8th, 1906. It is just possible, perhaps, that this was not a case of pernicious anæmia, for though the anæmia was severe and the colour index high for a severe anæmia, other than pernicious anæmia, it was not proved to have actually exceeded 1. Clinically, on the other hand, the diagnosis was pernicious anæmia. He was a married man with two children. He had been through the South African war, during which he suffered from enteric fever; and he had been home from South Africa for three and a half years, during all which time he had been out of work. He gave a history of having had rheumatic fever at 18 and pneumonia at 24, but of otherwise being sound and well— except for the enterica—until he felt himself to be getting physically weak a fortnight previous to his admission. He had " never been like this before." Ten days before his admission he had a shivering fit and took to bed; and he also suffered from headache, absent-mindedness and constipation. He was a dark-complexioned man, but showed the pale yellow tinge of pernicious anæmia cases—this colour had been spoken of by his friends as " jaundice." The urine was dark but clear, and no abnormal constituents were mentioned in it. The teeth were mostly carious, but the mouth was clean, for the patient had been in the habit of using potassium permanganate solution as a mouthwash. The spleen was readily felt coming down to the level of the umbilicus. The liver was not felt. The lungs and nervous system seemed natural. The heart was of natural size, but indeterminate systolic bruits—probably hæmic because they disappeared as the blood condition improved—were heard in all areas. The retinæ exhibited multiple

small hæmorrhages (Dr. Eason). Treatment was by arsenic, and improvement was considerable and rapid. The patient's wife writes on August 29th, 1907: " I write on behalf of my husband . . . who is at present time in Ontario. He writes saying he feels better since he been out there than he was at home. He been out there just over three months. He only done one week's work since he came out of Guy's till he started for Canada." The temperature chart showed practically no evening rises. The blood counts were as follows:—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Leitz.		Haldane.		Thoma Leitz.
8 October, 1906	1,525,000	30	30	1·000	3,200
5 Nov.	4,200,000	84	75	0·893	4,000

Note.—Many poikilocytes and many nucleated red corpuscles. S. 23, L. 6, P. 69, E. 2.

The temperature chart was as follows :—
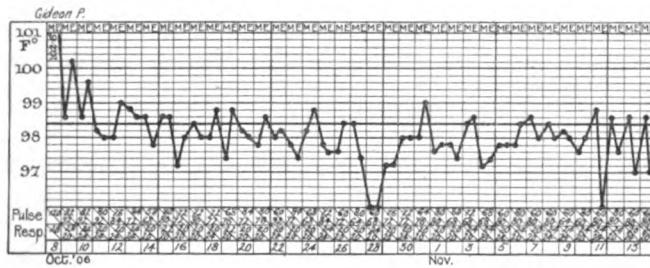
CASE 51.—Ref. No., Vol. 198, No. 304; Post-mortem No. 529, 1906.—Emma P., æt. 56, a housewife, was admitted under Dr. Taylor on August 22nd, 1906, and died on November 3rd, 1906. She was a married woman with one son. She had had a life of hard work, but had been perfectly well until two months previous to her admission, when she noticed that " her legs were swollen, and that she could not get her breath." Two weeks later she was obliged to take to her bed. When admitted she was orthopnœic, and very pale and ill. Her teeth had been very carious, and she now had a denture. Neither liver nor spleen was palpable. The nerves seemed natural. The heart was not increased in size, but there were hæmic bruits both at the impulse and in the pulmonary area. The urine was of specific gravity 1016, and it exhibited no obvious abnormality. The gastric juice contained abundance of free hydrochloric acid. On October 31st there were signs suggestive of fluid at the base of each lung ; on November 1st the patient became very drowsy ; on November 2nd she became comatose, and on November 3rd she died. At the autopsy the liver, kidneys and spleen all gave a well-marked Prussian blue reaction. There was œdema of the legs and thighs ; the body generally, and particularly the subcutaneous fat, was of a primrose yellow colour, and not at all emaciated. Each pleura contained nearly half a pint of serous fluid, and so did the pericardium.

There was no pericarditis. The heart weighed 391 grams. There was bright lemon-yellow fat in excess upon the surface, and thence infiltrating the muscle. The interior of the left ventricle exhibited well-marked tabby-cat striation. The liver weighed 1848 grams, exhibited the typical café-au-lait colour, and microscopically exhibited much fatty change in its cells. The spleen weighed 248 grams, but except for its size and its iron reaction looked natural, both macroscopically and microscopically. The kidneys were pallid, but otherwise, except for the iron reaction, did not look abnormal to the naked eye or microscopically. During life the pulse rate averaged 92, the respiration rate 24, and the temperature was raised each evening, except for a few days before death. The blood counts were as follows:—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Leitz.		Haldane.		
22 August, 1906	2,100,000	42	40	0·952	4,213
31 „ „	1,300,000	26	32	1·231	3,125
7 Sept. „	1,000,000	20	31	1·550	—
9 Oct. „	600,000	12	17	1·417	2,500

Note.—S. 34, L. 8, P. 52, E. 5, B. 1. There was one nucleated red cell for each 100 leucocytes.

The temperature chart was as follows:—
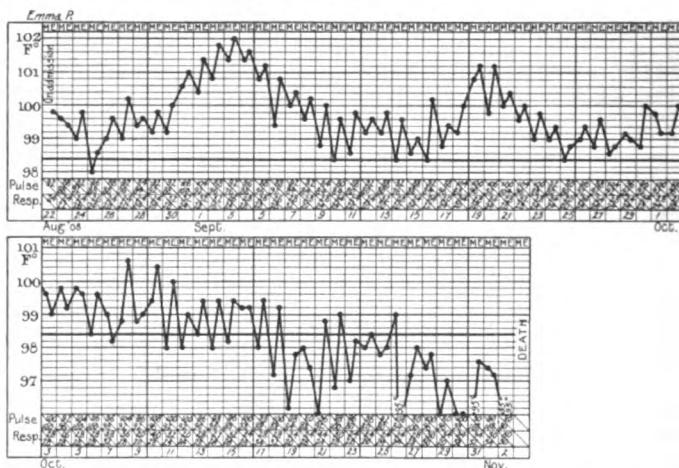
Case 52.—Ref. No., Vol. 199, No. 77.—Martha G., æt. 39, a cook, was under the care of Dr. Hale White from January 23rd, 1906, to April 25th, 1906. The main points of the case may be summarised as pernicious anæmia, vomiting, hæmoptysis, hæmatemesis, tyrosin found in the urine. She was an unmarried woman, but she had had one child. She looked well nourished, but she was extremely anæmic. She stated that she was well until the beginning of 1905, when she began to suffer from lack of strength,

vomiting, pallor, and severe diarrhœa. The vomiting became very severe unless she stayed in bed. She was sick four times a day if she tried to keep about, but when she went to bed the vomiting ceased. She was an in-patient in Guy's Hospital during 1905 for her abdominal symptoms, but the diagnosis of pernicious anæmia was not made at that time. She improved in health for a while, but soon after Christmas, 1905, she began to get rapidly worse again, so that she was quite unable to continue at work. On admission in 1906 she was a typical case of pernicious anæmia. The pulse rate, in bed, was about 80, her respiration rate about 20, and her temperature chart exhibited the very typical variations from normal or subnormal in the morning to 99° F., 100° F., or even 102° F. or 103° F. at night. There were hæmic bruits in all areas; the cardiac impulse was in its normal place. The urine contained urobilin, and yielded tyrosine crystals spontaneously in the centrifugalised deposit. Neither albumen nor blood were detected. The lung signs were normal; the optic discs and retinæ were natural; both liver and spleen were palpable. The right plantar reflex was persistently extensor, though the left was flexor, and there was no ankle clonus. The patient was greatly relieved when she was discharged in April, 1906, but by August, 1906, she had completely relapsed, and was at that time admitted to St. George's Hospital. The two new points noted at that time were, first, that she was very tender as to her bones at first, this tenderness becoming much less obvious after she had been in bed three weeks; and, secondly, that her spleen was very much larger than it had been in April, extending now across to the middle line and down to two and a half inches below the umbilicus. She slowly rallied again, and was discharged relieved at the beginning of October, 1906. The last news of her was that, " . . . She came home and lingered about until December, 1906, when she took to her bed and my doctor attended her, but she died in February, 1907, in the greatest agony with her heart, and pain in the nose and forehead, with bleeding of the nose and spitting of blood with thick phlegm. I have every reason to believe that my sister's illness was brought on by fright three years ago." The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Zeiss.		Haldane.		Thoma Zeiss.
25 Jan., 1906	1,500,000	30	35	1·166	2,200
31 „ „	1,060,000	21	40	1·905	6,200
8 Feb , „	1,560,000	31	42	1·355	10,000
16 „ „	1,280,000	26	40	1·539	8,000
22 „ „	2,120,000	44	42	0·954	7,700
1 March „	1,250,000	25	38	1·520	—
8 „ „	1,680,000	34	38	1·117	7,200
15 „ „	1,700,000	34	45	1·326	7,000
22 „ „	1,890,000	38	40	1·050	—
30 „ „	2,425,000	48	60	1·250	—
15 Aug. „	880,000	18	26	1·444	3,000
5 Sept. „	1,820,000	36	40	1·111	6,100
19 „ „	1,560,000	31	46	1·484	5,700
8 „ „	1,601,000	32	49	1·531	7,900

Note.—January 25th, 1906 : S. 40, L. 4, P. 49, E. 7. January 31st : Many poikilocytes and megalocytes, but no nucleated red cells seen. February 16th :

S. 35, L. 4, P. 57, E. 4.   March 15th : S. 38, L. 2, P. 58, E. 2 ; five nucleated red cells for each 100 leucocytes.   August 15th : S. 35, L. 3, P. 58, E. 3, M. 1.

The temperature chart was as follows :—
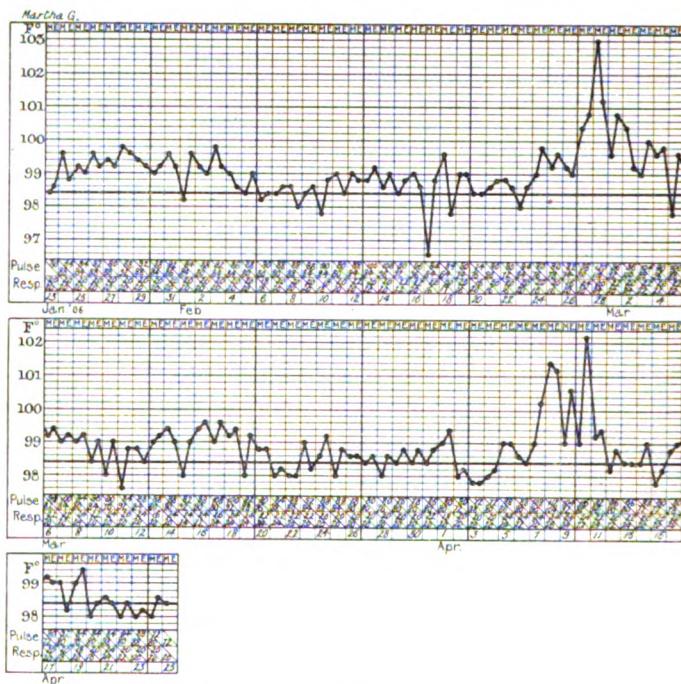
CASE 53.—Ref. No., Vol. 196, No. 188.—Annie B., æt. 33, a housewife, was admitted under Dr. Taylor on May 19th, 1906, and was discharged on August 3rd, 1906, relieved.   She had previously been in St. Thomas' Hospital from November, 1905, to January, 1906 ; and was re-admitted there from September, 1906, to November, 1906, when she died.   She was a married woman who had had one child and no miscarriage.   Her illness started eight months before her first admission to St. Thomas' Hospital, with an increasing general weakness.   She had also noticed puffiness of her ankles and feet, especially on walking, loss of appetite, dyspepsia, and a ringing in her ears. On admission she was a typical case of pernicious anæmia.   The heart was a little dilated, and there were generalised hæmic bruits and a bruit de diable in the neck.   The liver came one and a half inches below the ribs in the right nipple line.   The spleen was not felt.   There were no retinal hæmorrhages. There was widespread pigmentation of the skin in patches and in specks, and there was also *pigmentation of the buccal mucosa on the inside of the cheeks ;* this was confirmed at autopsy.   The pigmentation was not known to have antedated arsenical treatment, however.   The urine was high coloured, of specific gravity 1012 ; it contained neither albumin nor blood, but gave a well-marked urobilin band spectroscopically.   The temperature was ofte

99° F. to 100° F., the pulse rate 88 to 100, and the respiration rate 20 to 24. There were curious subjective sensations of paræsthesia, in particular in her thighs, which seemed to her at all times to "feel too hot inside and cold out" in a way which struck her as both abnormal, inconvenient and different to her sensations in other parts of her body. The behaviour of her knee-jerks is noteworthy. They were present on admission to St. Thomas' Hospital, but they had disappeared on December 21st, 1905, when liquor arsenicalis was being given in doses of ♏ix. The medicine was stopped, and the knee-jerks had returned on December 27th, 1905. Liquor arsenicalis in doses of ♏iii. was again given, and the knee-jerks were again absent on January 3rd, 1906. The had returned by the time of her re-admission in May. They were again absent in September, 1906. From Guy's Hospital the patient went to a convalescent home ; then relapsed and went to St. Thomas' Hospital. Pigmentation of the skin and buccal mucosa was very well marked. Pleurisy set in on the right side, and on November 11th, 1906, three pints of pleuritic fluid were withdrawn, followed on November 25th by another four pints. The patient collapsed and died on the night after the second aspiration. Post-mortem, purulent inflammation of the alveolar sockets with looseness of all the teeth were noted ; also pigmentation of the interior of the cheeks. There were shallow circular ulcers of the skin around the left patella. Acute pleurisy had occurred on both sides. The heart was not dilated, it was encased in the usual bright yellow fat, its valves were healthy, its muscle pale and soft. The liver was large, paler than normal, and gave a good Prussian blue reaction. The kidneys were markedly anæmic, and gave a slight Prussian blue reaction. The spleen was large, pale red, and gave some Prussian blue reaction. The marrow of the long bones was red. Micro-scopically, the marrow showed well-marked megaloblastic change. The heart exhibited pigmentary degeneration, fatty change, and slight mononuclear infiltration. The iron granules in the liver cells were chiefly at the periphery of the lobules. The spleen showed no fibrosis. The kidney exhibited catarrhal changes in the tubules and also iron granules in the epithelial cells. For notes of this case when in St. Thomas' Hospital I am indebted Dr. H. C. Squires. The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpus-cles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index	Leucocytes, per cub. mm.
18 Nov., 1905	981,280	19	25	1·316	– –
30 „ „	843,750	19	20	1·052	—
12 Dec., „	1,100,000	22	25	1·136	—
30 „ „	2,231,250	45	40	0·888	—
4 Jan., 1906	3,325,000	66	50	0·757	—
20 May, „	1,800,000	36	40	1·111	—
8 June, „	2,000,000	40	25	0·625	—
19 „ „	2,040,000	41	35	0·854	—
29 „ „	2,640,000	53	40	0·755	—
20 July, „	3,800,000	76	—	—	—
5 October .	679,687	13	20	1·539	—
18 „ „	1,178,125	23	25	1·087	—
11 Nov., „	1,259,400	25	25	1·000	—

Note.—18th November, 1905, to 4th January, 1906: Normoblasts and at least one megaloblast seen at each count except the last. 20th May, 1906: Poikilocytosis very marked, and many nucleated red cells seen.

The temperature chart was as follows :—
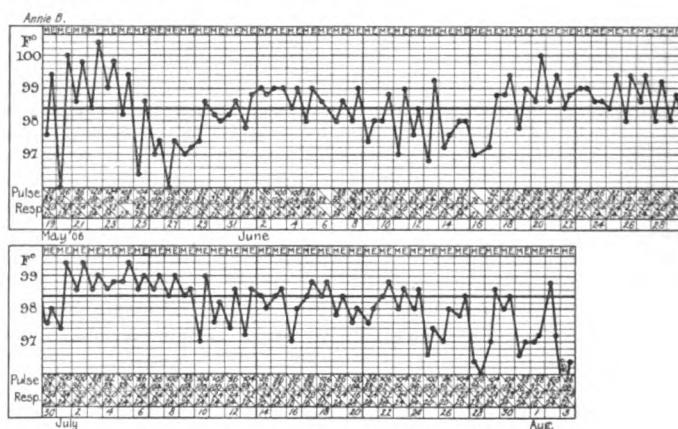
CASE 54.—Ref. No., Vol. 196, No. 366.—Frank B., æt. 48, a commission-aire, was admitted under Dr. Taylor on October 1st, 1906, for œdema and pains in his legs, and was sent to an Asylum for the Insane on December 21st, 1906. He was a married man with seven children. He was in the Army in India for six years, and suffered from dysentery. About four months before his admission he had much bleeding from what were regarded as piles. It was nine months before admission, however, that he first began to ail from swelling and pain in the right leg from knee to ankle ; two months after which he began to get short of breath, and he rapidly became so weak that he was soon unable to remove his own boots. He was still well covered with fat, but he stated that he had been getting thinner. His teeth were carious ; his general appearance was that of a case of pernicious anæmia, and this was confirmed by the blood counts. He developed delusions, however, and became very impulsive and dangerous, so that he had to be removed to an asylum as a case of mania in addition to pernicious anæmia. Neither liver nor spleen could be felt. The lungs were natural. There were neither retinal nor other hæmorrhages. The peripheral nervous system seemed natural. The urine was amber yellow, of specific gravity 1020, acid, and free from albumin and blood. The report from Cane Hill Asylum on August 15th, 1907, was as follows :—" Frank B. Mental condition.—Dull confused appearance. Talks to himself. Is actively hallucinated, both auditory and probably visual. Talks incoherently about ' pice,' ' mines just over the hill.' Uses a number of native Urdu words. Mixes identities. Fails even to recognise his wife who visits him. Orienta-tion very bad ; no idea of time or place. Has neglected calls of nature, and requires much care and attention. Urine pale lemon colour, specific gravity

1009, acid. No bile pigment, albumin or sugar.'' The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Leitz		Haldane		Thoma Leitz
4 Oct., 1906 ...	1,225,000	24	38	1·583	8,000
19 ,, ,, ...	2,500,000	50	—	—	8,000
21 Nov., ,, ...	3,573,800	71	78	1·099	—
12 Dec., ,, ...	3,200,000	64	74	1·157	—

The temperature chart was as follows :
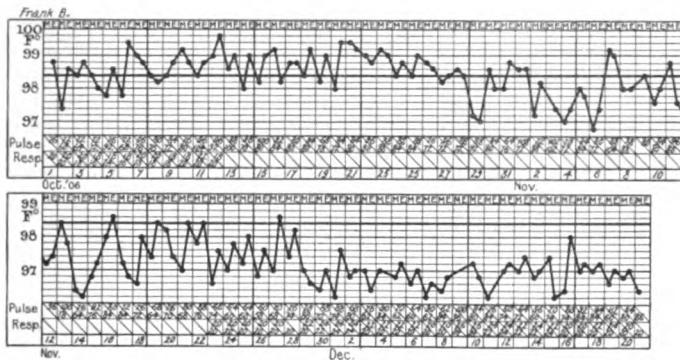
CASE 55.—Ref. No., Vol. 197, No. 270.--Matilda W., æt. 51, a domestic nurse, was under Dr. Hale White from June 18th, 1906, to August 11th, 1906. She was admitted for anæmia, weakness, and palpitations of the heart. An unmarried woman, she had always enjoyed good health and comfortable surroundings in the service of a wealthy family. A year and a half previous to her admission she caught whooping-cough from the children she was in charge of, and this caused the appearance of a large femoral hernia, which was operated upon successfully in Sweden at Christmas, 1905. She said she had never been well since the operation, but had gradually become physically weaker and more anæmic, with loss of appetite and liability to palpitations of the heart. She also began to suffer from attacks of what she called '' bilious vomiting,'' without diarrhœa, and before she took to her bed there had been some œdema of the ankles after walking or standing long. She also had curious pains in the legs from the knees downwards, which she compared to '' those caused by walking in deep snow.'' She was quite a cheerful person, typically lemon-yellow in colour, and fairly well covered. The urine was pale in colour, of specific gravity 1009, and it contained neither albumin nor blood ; urobilin is not mentioned. The lungs were natural. The heart was of natural size, but

exhibited hæmic bruits in all areas.   The spleen and the liver were not palpable.   The reflexes were natural.   The teeth were "bad," and the tongue white and coated.   The respiration rate usually lay between 20 and 24, the pulse rate, when in bed, between 70 and 90, and the slight daily pyrexia, up to 99° F. or 100° F., was well marked.   Treatment was by liquor arsenicalis, which was increased up to a dose of ♏ix.   The patient returned home greatly improved in health, but she relapsed next year.   The following was the reply to inquiry in August, 1907 :—" Miss W. has been ill off and on since her discharge in August, 1906.   Since November, 1906, she has been treated by several doctors, one specialist saying she might live until June, 1908, if she kept quiet and calm.   At present she is very ill, and unable to write herself."   This is the last that was known of her.   The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	White corpuscles, per cub. mm.
21 June, 1906	1,237,500	25	33	1·320	6,146
23 „ „	1,250,000	25	35	1·400	6,770
16 July, „	1,950,000	39	36	0·923	—
8 Aug., „	3,340,000	67	67	1·000	7,500

Note.—June 23rd : S. 24, L. 5, P. 69, E. 2.   July 16th : S. 24, L. 9, P. 67, E. 0.

The temperature chart was as follows :—
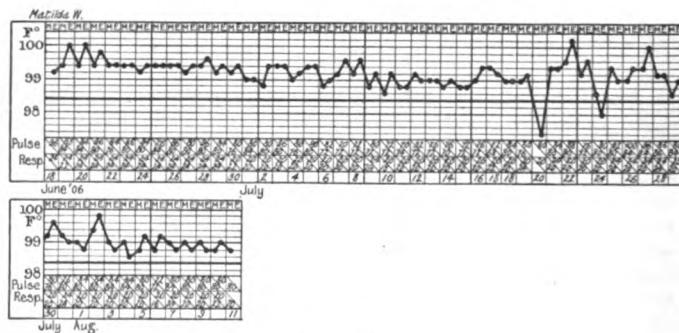
CASE 56.—Ref. No., Vol. 201, No. 247.—George M., æt. 50, a lithographic draughtsman, was under Sir Cooper Perry from 29th June to 17th August, 1906. Agnes P., of the same address, writes that " Mr. M. died in November, 1906." He was a married man with two children.   He had been born in Jamaica, but had lived in England since he was 10 years old ; at first he had always been suffering from severe coughs and colds.   Afterwards he had been well until shortly before his admission.   Notwithstanding his occupation, he had

had nothing to do with lead, and was admitted for "general debility." He had been taken three years previously with pains in his back and chest, and these pains got worse and extended to the buttocks and legs. Lately there had been increasing anæmia with shortness of breath and some impairment of vision. There had been no particular gastro-intestinal symptoms until recently, when retching and flatulence without vomiting developed. The patient had done no work for two months previously, for he was unable to endure any fatigue. The death of his mother two weeks previous to his admission had made his general condition worse. When seen he was very anæmic indeed, but not very yellow. There was no general pigmentation of his body, but there were many brown spots on his left elbow and on both his big toes. There was no pigmentation in the mouth. The heart was of natural size, but there was a hæmic bruit at the impulse. The lungs were natural, the teeth were very septic and outstanding from the gums, and the tongue was furred and white. The lower edge of the liver could be just felt, and the spleen was just palpable. The knee-jerks and other reflexes were natural. The urine had a specific gravity of 1016. It contained no albumin. After arsenical treatment was adopted vomiting became very troublesome. The patient suffered from a good many symptoms which were regarded as neurotic. The pulse rate averaged 80 to 104, the respiration rate 20 to 24. The temperature chart was a typical one, with evening rises to 99° F. or 100° F. Towards the end of his stay in hospital the spleen was felt one inch below the ribs. The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Leitz.		Haldane.		Thoma Leitz.
3 July, 1906	1,790,000	38	—	0,948	6,980
10 „ „	2,215,000	44	36	9,750	4,320
16 „ „	1,160,000	23	33	1,739	5,000
24 „ „	1,550,000	31	40	1,107	3,600
31 „ „	1,200,000	24	34	1,333	6,250
7 Aug. „	1,600,000	32	32	1,062	—
14 „ „	1,300,000	26	35	1,346	3,500

Note.—July 3rd : Blood films showed marked poikilocytosis and polychromasia, in addition to which there were nucleated red corpuscles and many megalocytes. The differential leucocyte count was as follows :—S. 34, L. 12, P. 52, E. 0, B. 2. July 10th : Films show many megalocytes, microcytes, and poikilocytes. The differential leucocyte count was as follows :—S. and L. 28, P. 69, E. 2, B. 1. July 24th : There were more normocytes than before, but there were still many poikilocytes and megalocytes ; and four nucleated red corpuscles were counted to every 100 leucocytes. The differential leucocyte count was as follows :—S. 27, L. 13, P. 56, E. 3, B. 1. August 13th : Nucleated red cells were still present. The differential leucocyte count was as follows :—S. 32, L. 8, P. 57, E. 3.

The temperature chart was as follows :—
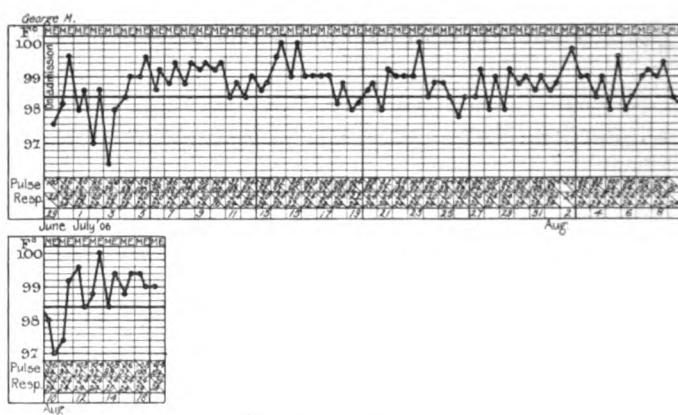
CASE 57.—Ref. Nos., Vol. 201, No. 52 ; Vol. 206, No. 337; Vol. 208, No. 373; Vol. 214, No. 3.—William L., æt. 44, a railway porter, was under Dr. Fawcett, from January 9th, 1906, to March 29th, 1906, when he was discharged, to be re-admitted on May 21st, 1907, and re-discharged on July 7th, 1907. He was under Dr. Beddard from August 29th, 1907, to October 6th, 1907 ; and under Dr. Hale White from November 16th, 1907, to February 21st, 1908. He had been born in Cheshire, and had lived in London for the last twenty years. Eight months previous to his admission in 1906 he complained of increasing weakness, and of progressive loss of weight, shortness of breath, and occasional attacks of abdominal pains. He also had epistaxis from time to time, and if he walked much he had some puffiness of his feet and ankles. His blood condition improved enormously, and the patient was discharged apparently well. The only points to note about him beyond the blood condition were that his urine contained urobilin to the spectroscopic test, and he bore arsenical treatment well, the dose being increased up to eight minims of the liquor thrice daily, and that the gastric juice was deficient in H.Cl. He went from Guy's Hospital to a convalescent home at Swanley, and on his return from there he continued his work for five months, feeling perfectly well all that time. He then relapsed, and attended the Out-patient Department, but managed to continue his work until Christmas, 1906. He then had to give up, as he felt too weak to continue. Moreover, if he tried to walk his legs became very painful and swollen. His colour had previously been very fair, but now it became a typical yellow. There had been epistaxis on several occasions again. There had been no vomiting ; there was a marked tendency to constipation. The teeth were not in a very bad condition, but several of them were decayed, and they were not absolutely clean. The retinæ exhibited hæmorrhages, and urobilin was again found in the urine. The reflexes were natural. Neither liver nor spleen was felt. The temperature chart showed much the same sort of slight pyrexia, as most of these

cases do. He was discharged much relieved, and stayed with some friends in Yorkshire for three weeks; during the third week he began to feel weaker and lost his appetite. On his return to London he was one of Dr. Fawcett's out-patients, and was treated with arsenic, malt and iron. On re-admission he was of a typical lemon yellow colour; the spleen was palpable; the liver was not felt; the heart was of normal size, and no bruit was heard. The lungs were normal and the nervous reflexes were natural. He relapsed again, and was re-admitted upon November 16th, 1907, to be re-discharged upon February 21st, 1908. Treatment was again by means of arsenic. At first upon this occasion diarrhœa replaced the former constipation, but otherwise there was little fresh to note. He discharged himself against advice. The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes, per cub. mm.
	Thoma Leitz.		Haldane.		Thoma Leitz.
13 Jan., 1906	1,500,000	30	—	—	4,400
15 „ „	1,892,000	38	52	1·369	3,475
7 Feb., „	2,600,000	52	62	1·192	6,250
5 March, „	5,450,000	109	75	0·688	4,600
21 May, 1907	1,400,000	28	28	1·000	5,600
28 „ „	2,100,000	42	38	0·905	—
13 June, „	2,100,000	42	48	1·143	—
19 „ „	3,200,000	64	55	0·860	—
26 „ „	3,500,000	70	60	0·857	3,600
29 August, „	1,982,000	40	45	1·125	3,960
14 Sept., „	1,500,000	30	40	1·333	—
6 Oct., „	2,458,333	49	60	1·224	—
18 Nov., „	1,500,000	30	40	1·333	—
16 Dec., „	3,000,000	60	60	1·000	—
3 Jan., 1908	2,500,000	50	38	0·760	—
16 „ „	1,500,000	30	50	1·666	—
30 „ „	1,300,000	26	55	2·115	—
8 Feb., „	800,000	16	40	2·500	—
9 „ „	900,000	18	40	2·222	—
12 „ „	1,500,000	30	40	1·333	—

Note.—January 15th, 1906: Films showed many poikilocytes. February 7th, 1906: Poikilocytes and megalocytes both numerous. May 21st, 1907: Poikilocytosis well marked. June 13th, 1907: Fair numbers of megaloblasts and normoblasts. June 19th, 1907: The differential leucocyte count was noted as being natural. January 9th: The differential count was as follows :— S. 30, L. 3, P. 63, E. 1, B. 3. February 3rd: S. 35·7, L. 3·6, P. 60·7, E. 0, B. 0. June 13th: S. 27, L. 2, P. 65, E. 3, B. 3. August 29th: S. 23, L. 4, P. 72, E. 1, B. 0, M. 0. Poikilocytes were marked in the films. Three nucleated red corpuscles to each film. November 18th, 1907: Poikilocytes very marked; no nucleated red corpuscles. November 30th, 1907: Poikilocytes very numerous; still no nucleated red corpuscles seen. February 6th, 1908: Patient very much weaker on account of diarrhœa. Cacodylate of soda in one grain doses given subcutaneously.

The temperature chart was as follows :—
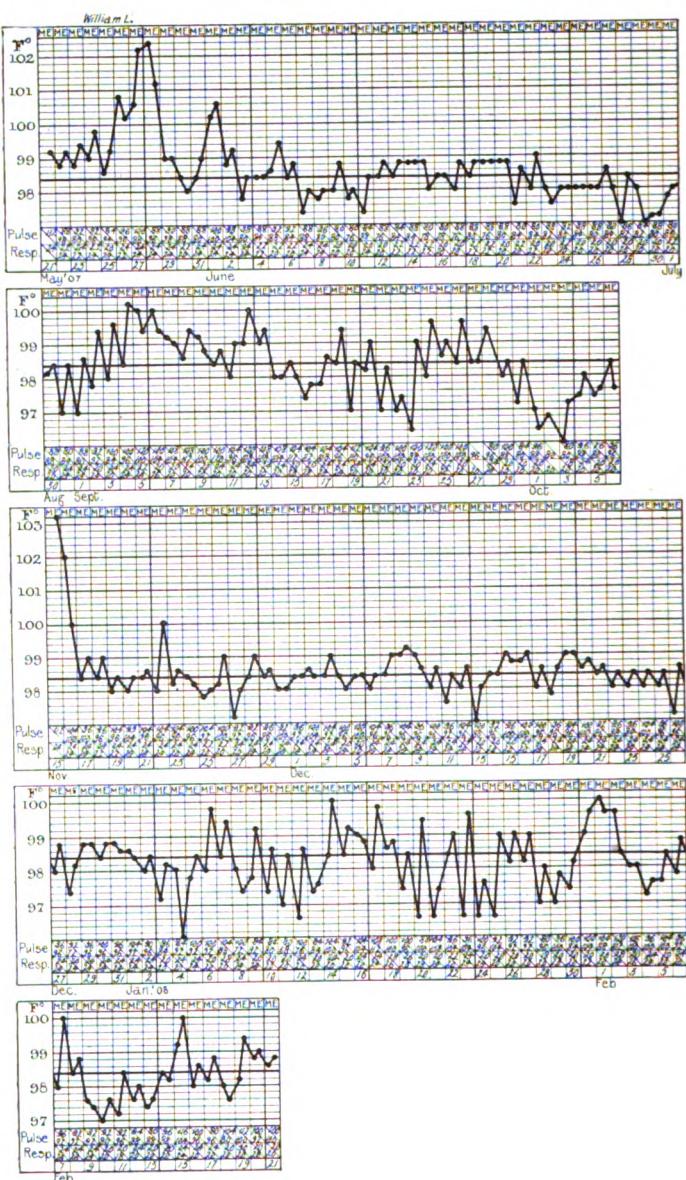
CASE 58.—Ref. No., Vol. 204, No. 363; Post-mortem, No. 469, 1907. Robert M., æt. 49, a carman, was admitted under the care of Dr. Shaw on September 27th, and died September 29th, 1907. He came in for pains in the abdomen and for sickness. He had never been ill previous to his present illness. He began to feel unwell twelve months ago. During the last two months he had been definitely worse, being unable to retain any food. He had been accustomed to take beer, but this now so irritated his stomach that he was obliged to give it up. Formerly the food would remain in the stomach for half a day before being vomited, now it was often brought up within a few minutes of being swallowed. The only thing he could keep down was plain water. He had never seen blood in his vomit, nor passed any per rectum, but he had often suffered from epistaxis. His bowels had been moved regularly. He had suffered from a rather troublesome cough lately, whilst at the least exercise he became short of breath. He looked thin, weak, and anæmic, with the typical lemon-coloured skin. He was first admitted to the surgical side, into Naaman Ward, under the impression that he had some surgical gastric lesion, but was transferred to the medical side. The heart was decidedly hypertrophied, but there were no definite bruits. The lungs were normal. As regards the teeth, they were not good. The stomach was not dilated. The liver could be felt three and a half inches below the costal margin, and it was smooth. The spleen was palpable. The urine was straw-coloured, acid, and had a specific gravity of 1008; it contained a small quantity of albumin. The patient died of heart failure. At the post-mortem examination the lungs were pale and œdematous. There was recent pleurisy at the right apex, with recent pneumonia beneath it. There was early pericarditis. The heart was hypertrophied, weighing 652 grams. The mitral valve was stenosed, and the aortic valves were thick and bore recent vegetations. The spleen weighed 417 grams, and there was recent capulitis over it. The kidneys weighed 372 grams, and they were pallid. The liver gave a very well-marked blue ferrocyanide reaction. The bone marrow of femur was red. The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Leitz.		Haldane.		Thoma Leitz.
27 Sept. 1907	1,700,000	34	35	1·030	—
28 „ „	1,650,000	33	—	—	25,000

Note.—The differential leucocyte count was as follows : S. 10, L. 3, P. 84, E. 2, B. 1, M. 0.

No temperature chart is available in this case.

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CASE 59.—Ref. No., Vol. 204, No. 402.—Hodgkin H., æt. 46, a dentist, was admitted under the care of Dr. Shaw, October 30th, 1907; and was discharged *in statu quo* on November 7th, 1907. The patient was a widower; he came in for diarrhœa and vomiting. He had suffered from symptoms which he called dyspepsia for four or five years, but he took little or no notice of this until four months before admission. Previous to this he had only suffered from some discomfort after meals, but for the last four months there had been diarrhœa and vomiting, the latter invariably taking place

after meals. He had once or twice noticed a little blood in his motions, and
he had had piles. He saw several doctors, and finally came into the hospital,
having lost 2 stone in weight in the four months owing to absence of appetite
and inability to keep down his food. For some time past he had noticed
himself getting out of breath quickly. He was a well-nourished man,
apparently of good weight for his size. His complexion was a typical lemon
colour. His teeth had been in good order until four months ago, but now
they were not so good, and there were very sore and ulcerated places in the
inner side of his cheeks where the bad teeth were. The liver dulness extended
for 1 inch below the costal margin, but the liver itself could not be felt. The
spleen was not felt. The heart was of normal size, and there were no bruits.
The lungs were normal. The urine had a specific gravity of 1020; it was
alkaline and highly coloured. The temperature was typical. The pulse rate
varied between 82 and 108, and the respiration rate between 22 and 26.
Diarrhœa was very troublesome, motions being passed as often as ten times in
twenty-four hours. The blood count was as follows:—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
13 Oct., 1907	2,850,000	57	60	1·053	1,800

Note.—On November 7th the differential leucocyte count was as follows:—
S. 54, L. 8, P. 31, E. 0, B. 7. The patient was discharged at his own request
with his condition unaltered. Owing to the diarrhœa it was impossible to
give arsenical treatment.

The temperature chart was as follows:—
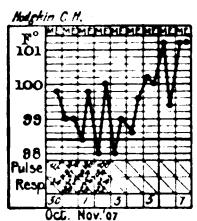
CASE 60.—Ref. No., Vol. 204, No. 352.—Frances M., æt. 52, a married
woman, was admitted under Dr. Shaw on October 11th, 1907, and discharged
in statu quo on November 4th, 1907. She died at home on December 4th,
1907. She came in for shortness of breath. She was the mother of four
children, and had had no illnesses at all until the present trouble began two
years ago, when she noticed her feet swelling, and found herself short of
breath on ordinary exertion. She could attribute this to no cause. She kept
on with her work until ten months ago, when she first saw a doctor, and she
had been in bed almost all the time since. It was about two months ago
that she noticed her colour changing. For the last ten months the patient
had had occasional vomiting, once or twice a week, and she had also been
much troubled with throbbing in the head, and pain in the region of her ears,

and sleeplessness, for which she had been taking draughts. Two years ago, just before she knew she was so ill, she had had all her teeth removed and a false set made, on account of "dyspepsia." She had lost weight during the last two months. There has been no loss of blood. She had a typical lemon-yellow skin. There was slight pyrexia. There was some slight œdema of the chest and loins, but not of the legs. The heart exhibited well-marked universal hæmic systolic bruits. There were a few râles at both bases, and there was deficient vascular murmur at the apex of the left lung, while at the base of the left lung there was marked dulness and deficiency of vesicular murmur as high as the eighth rib. The liver could be felt three inches below the costal margin. The spleen was not felt. The urine was cloudy, acid, and had a specific gravity of 1011; it contained no albumin or blood, but gave a definite urobilin band spectroscopically. The bowels were open rather too freely. There were no retinal hæmorrhages. Treatment was at first by liquor arsenicalis, but diarrhœa became so troublesome that it had to be stopped, and catechu, kino and opium given instead. The blood counts were as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes, per cub. mm.
15 October, 1907	1,000,000	20	30	1·500	—
18 „ „	917,900	18	25	1·388	4,400

Note.—26th October.—The differential leucocyte count was as follows:—S. 65, L. 9, B. 24, E. 2. Films showed many microcytes, megalocytes and poikilocytes. Nucleated red corpuscles were present to the extent of 259 per cub. mm.

The temperature chart was as follows :- -
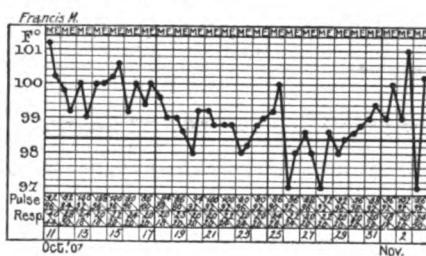
CASE 61.—Ref. No., Vol. 207, No. 423 ; Post-mortem No. 436, 1907.—Alice S., æt. 35, was admitted under the care of Sir Cooper Perry, on October 9th, 1907, dying upon October 18th, 1907. She was admitted for shortness of breath and general malaise. She had married at twenty-one, and had had four children, the youngest of whom was now four years old ; there had been no miscarriage. The patient had been accustomed to work hard in the fields, sometimes as much as ten hours a day, and she did not remember having had any illness except the present one. For the past two or three months she had not felt in her usual state of health, although she could not say that she felt ill. A month ago she felt so weak that she was unable to do her work. She vomited after food, and her skin changed from a rosy colour to a lemon yellow. Headaches were a very troublesome

symptom. There was never any swelling of the feet, and she said she had not wasted at all. She finally called her doctor in, and he diagnosed that her trouble was due to her teeth. There had been trouble with the latter during the last two years, during which time several had been extracted, and there had been an alveolar abscess. She was of the typical colour. The temperature chart was even more marked than in most pernicious anæmia cases, corresponding with the serious condition of her health. The heart was of natural size, and no bruits were heard. The lungs were natural. The teeth, as mentioned, were in an extremely bad septic state, with many stumps. The spleen was not palpable. The liver could just be felt below the ribs. The nervous reflexes were natural. The urine was of an amber colour, slightly cloudy, acid in reaction, and it had a specific gravity of 1022. No albumin was present. Several teeth were removed on October 11th, when a quantity of blood was lost, and it seemed as though the downhill course was accelerated by the teeth extraction. Shortly before death many subcutaneous hæmorrhages appeared. She lapsed into a semi-comatose condition, and died quietly. Treatment had been by means of stimulants and mouth washes, liquor arsenicalis, and saline infusions per rectum. The post-mortem report states that the subcutaneous fat was very yellow ; that there were sub-epidermal hæmorrhages and also petechiæ under the peri- cardium and under the endocardium. The bone marrow of the femur was deep red. The heart was dilated on the right side, and the myocardium exhibited well-marked tabby-cat striation, particularly in the musculi papillares. The kidneys, spleen and liver all gave a good Prussian blue reaction for iron. The kidneys were marked with a few scars, apparently the result of former infarcts. The spleen was enlarged, and the liver had a typical pale chocolate colour. The blood counts were as follows :—

Date.	Red corpuscles per cub. mm.	Red corpus-cles per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes, per cub. mm.
10 October, 1907	1,800,000	36	36	1·000	6,000

Note.—Films showed nucleated red corpuscles, and many poikilocytes and megalocytes.

The temperature chart was as follows :—
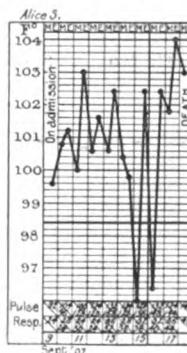
CASE 62.—Ref. No., Vol. 210, No. 365.—Peter S., æt. 42, a baker, was admitted under the care of Dr. Hale White on August 26th, 1908, and discharged relieved on October 13th, 1908. He had worked hard as a baker, and was of very temperate habits. He had been in Stephen Ward under the care of Dr. Pitt eleven years ago, at which time he remained in the hospital seven weeks, and his disease was diagnosed as dyspepsia, part of the treatment consisting in the removal of a number of teeth. Since that time he had been quite well until six months before his admission, when he had an attack of diarrhœa, and at the same time passed blood per rectum. This is the only time that he had done so. He had never vomited, his bowels had been regular, and he was never troubled with flatulence. Since his present trouble started his appetite had been very poor, and he had lost weight considerably. From the time of the diarrhœa, six months ago, until the present time his illness had come upon him progressively, but slowly. He was now very anæmic and feeble, even the slightest exertion being a trouble to him, and he was short of breath unless he lay still. The heart was of normal size, and exhibited no bruits ; the lungs seemed natural. The liver could be felt two inches below the costal margin ; it was smooth. The spleen could not be felt. The urine was acid in reaction, and was a pale straw colour ; had a specific gravity of 1013, and contained no albumin and no indican. The nervous reflexes were natural. He complained of weakness in every joint and of "deadness" in the region of the joints. Treatment was by liquor arsenicalis, which was increased up to 11 minims three times a day. On discharge the man felt comparatively strong and well, but the skin still retained its lemon tint. There was no pyrexia at all in this case, except during the first five days, when the temperature reached 99 or 99·4 in the evening. The pulse rate averaged 64 to 80, the respiration rate 20 to 24. The blood counts were as follows:—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes, per cub. mm.
28 Aug., 1908	2,500,000	50	50	1·000	5,C00
4 Sept. „	2,800,000	56	70	1·250	—
5 „ „	2,800,000	56	75	1·340	---
7 . „	2,900,000	58	75	1·293	—

Note.—On examination the films showed microcytes and megalocytes ; a number of megaloblasts were also seen. The urine contained urobilin.

The temperature chart was as follows :—
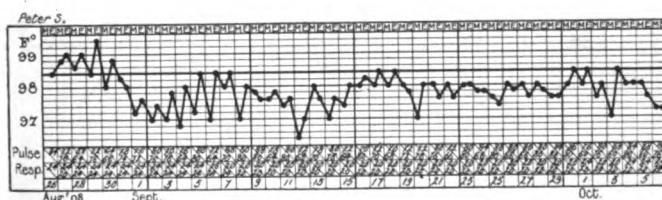
CASE 63.—Ref. No., Vol. 210, No. 238 ; Post-mortem No. 265, 1908.—Ada B., 37, was admitted under Dr. Hale White on May 9th, 1908, and died May 20th, 1908. She came in for vomiting and for general weakness. She had lived the greater part of her life in a healthy country district, but she had never been a very robust woman. She had been a general servant until she was married at 24, at which time she had her first attack of vomiting and weakness, and her doctor then told her that she had an ulcerated stomach. She had not to her knowledge passed blood per rectum or by mouth. From that time, which was thirteen years ago, except for not being very strong, she had remained fairly well until October, 1907, when "the symptoms of her old complaint," as she said, returned. She became tired, lost her appetite, and if she did take any solid food it was vomited up again shortly afterwards. Even when only taking milk, she vomited ; and often blood would come up. The vomiting was always shortly after food, and it was accompanied by pain in the upper part of the abdomen. The symptoms had gradually got worse, until six weeks ago she had been obliged to call her doctor in, and he diagnosed gastric ulcer and treated her for this as before. This relieved her vomiting, but not her general condition, so she was sent to the hospital and admitted. She was a typical lemon-yellow colour. There was marked evening pyrexia. The heart was not enlarged, and there was no bruit, unless a doubtful systolic bruit in the pulmonary area. The lungs were normal. The liver could be felt three-quarters of an inch below the costal margin. The spleen was easily palpable and very firm. There were no abnormal gastric signs. The nervous reflexes were natural. The ophthalmoscope showed numerous small retinal hæmorrhages. Arsenical treatment was adopted. Shortness of breath was very marked, and there was precordial pain, which ultimately turned out to be due to pericarditis, of which she died. The post-mortem examination showed that all the organs were pale and the fat was a bright yellow colour. The thyroid gland presented adenomatous enlargement. The lungs were pale, but otherwise quite normal except for some compression by pericarditis. The heart weighed 356 grams, and it was big and dilated ; there was typical pericarditis with many small hæmorrhages, both in the pericardium and also under the endocardium, and also tabby-cat striation, but no valvular lesion. The spleen weighed 500 grams, and contained three infarcts. The kidneys were pale and exhibited several small infarcts. The liver was large, and both the liver and spleen gave a good Prussian blue reaction. The bone marrow of the femur was a deep red colour. The brain showed no abnormality beyond a few submeningeal petechiæ. The blood count was as follows :—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes, per cub. mm.
10th May, 1908	950,000	19	30	1·583	—

Note.—No very marked degree of poikilocytosis.

The temperature chart was as follows :—
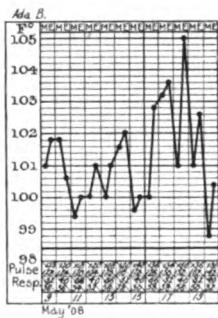
CASE 64.—Ref. No., Vol. 211, No. 367.—John G., æt. 40, a shunter on the railway, was admitted under Dr. Pitt upon September 15th, 1908, and was discharged relieved on November 4th, 1908. He was a married man with a wife and four children. He was born at Redhill, Surrey, and entered the Army in 1888, and up to that time had never been ill. He volunteered for service in India in 1889, and served there for five years. Whilst in India he had an attack of ague. He was seven months in Egypt, and was again troubled with attacks of ague. He returned home in 1895, and in 1899 went out to Africa, serving in Swaziland. Whilst there he was laid up for three months with a very severe attack of malaria. He attributes his illness to the dirty water they had to drink, which he says "was as thick as coffee." He returned to England in 1900, and began work on the South-Eastern Railway. He admits having had gonorrhœa in 1893, but denies any history of syphilis. He traces his present complaint from his attack of malaria in 1900. He was invalided home, but recovered sufficiently to take up work as a shunter. Three years before his admission to Guy's Hospital he was seized with "an attack of the shivers," and could not keep warm. His skin went very yellow about this time, and he attended as an out-patient at Guy's Hospital, and was relieved after having been sent to a convalescent home at Seaford. After the lapse of a few months, however, his illness recurred several times. The present bout of illness began five weeks before his admission, commencing with attacks of shivering as before, together with diarrhœa and extreme weakness. He noticed that his feet and calves were much swollen, and he could not work ; he came to the hospital and was admitted. The skin was a decided lemon-yellow colour, but the sclerotics were white. The teeth were in a decayed state, but the mouth otherwise was clean. The liver was felt half an inch below the costal margin, but the spleen was not felt. The lungs were natural. The heart exhibited well-marked signs of aortic regurgitation. The urine had a specific gravity of 1015, was acid and a reddish yellow colour. Dr. Pitt diagnosed pernicious anæmia and aortic incompetence. Treatment was by liquor arsenicalis, which was increased up to eight minim doses three times a day. The general improvement in the appearance of the patient and his general feeling of increased strength were much greater than is indicated by the blood counts. The temperature chart was a typical one, reaching to upwards of 101° F. each evening for the first few days, then to

between 99° F. and 100° F., and finally remaining normal when improvement had set in. Only the latter part of the chart is given below. The pulse rate varied from 72 to 104, and the respiration rate was about 24. The blood counts were as follows:—

Date.	Red corpuscles, per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes, per cub. mm.
	Thoma-Leitz.		Haldane.		
20 Sept., 1908	687,000	14	17	1·214	—
7 Oct., „	1,650,000	33	37	1·121	—
15 „ „	1,258,000	25	32	1·280	—
26 „ „	1,500,000	30	34	1·133	—

Note.—Blood films showed poikilocytes, many megalocytes, some nucleated red corpuscles and polychromatophilia.

The temperature chart was as follows:—
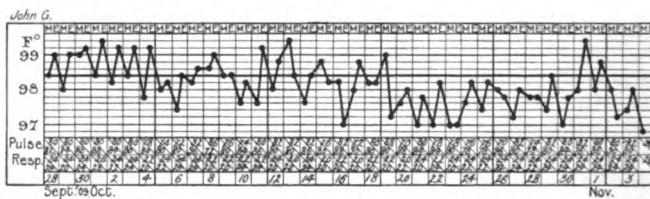
CASE 65.—Ref. Nos., Vol. 213, No. 129; Vol. 214, No. 418; Post-mortem No. 401, 1908.—William R., æt. 45, an upholsterer, was admitted under Dr. Hertz on March 13th, 1908, being discharged relieved, and able to work, on June 12. to relapse and be readmitted under Dr. Fawcett on July 21st, 1908, dying on August 19th, 1908. He had been in very good health up to the beginning of his present illness. He had been married twelve years. His trade had always been upholstery, he had always been in good circumstances, and he had not been abroad. About 18 months before his first admission he began to notice that he was more short of breath than usual. He had been gradually getting worse up to the present time. About 12 months ago his eyesight began to fail. His doctor could find nothing wrong with his eyes, and glasses had no effect. It was thought to be tobacco amblyopia which had improved considerably during the last few months. He had to give up his work at Christmas, 1907. For the last few months he had noticed that his hands and feet seemed to be numbed. For a few days previous to his second admission his feet had been swelling. Treatment was by arsenic. He had an extremely pale yellow skin, and it was pigmented in specks and spots. There was some slight œdema of the abdomen and front of the sternum, and a slight lumbar cushion. There was also slight œdema of the ankles continuing as far as the knees. The lips and gums were very pale, the mouth and teeth were clean, though many of the latter were carious. The lungs exhibited signs of œdema at both bases. The respiration rate averaged about 24, until shortly before death, when it rose to 36. The pulse rate varied from about 72 to 96, and shortly before death rose to 156. The temperature chart was typical, evening pyrexia becoming less as the man improved during his first stay in hospital, but returning during the relapse, whilst just before death it rose to 105° F. The heart was of normal size; sometimes it exhibited hæmic bruits, at other times it did not. The spleen came just below the costal margin, and the liver three-quarters of an inch below. The numbness in the hands and knees diminished. The nervous reflexes seemed natural. Shortly after hyper-

pyrexia had set in, the patient became comatose with a subnormal temperature, and died from respiratory failure. The post-mortem examination showed œdema of lungs, and recent acute pericarditis without free fluid, and tabby-cat striation of the heart muscle. The liver exhibited the typical Prussian blue reaction. The bone marrow of the femur was like red currant jelly in colour and consistency, and microscopically it showed numerous nucleated red cells in every stage of formation. The blood counts were as follows :—

Date.	Red corpuscles per cub. mm.	Red corpuscles per cent. of normal	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes per cub. mm.
	Thoma Leitz.		Haldane.		Thoma Leitz.
14 March, 1908	750,000	15	20	1·333	3,125
2 April, „	1,350,000	27	45	1·666	4,000
28 „ „	2.440,000	49	72	1·469	5,160
8 July, „	1,400,000	28	21	0·750	—
4 August, „	1,400,000	28	40	1·428	3,600
9 „ „	—	—	—	—	20,000

Note.—The differential leucocyte count was as follows :—S. 62, L. 1, P. 37, E. 0. In films, both on April 2nd, and on July 8th, there was marked poikilocytosis, and polycromatosis. Megalocytes were abundant. There were also numerous megaloblasts, some with lobulated nuclei, and a few normo-blasts. Basophilia of the red cells was very marked.

The temperature chart was as follows :—
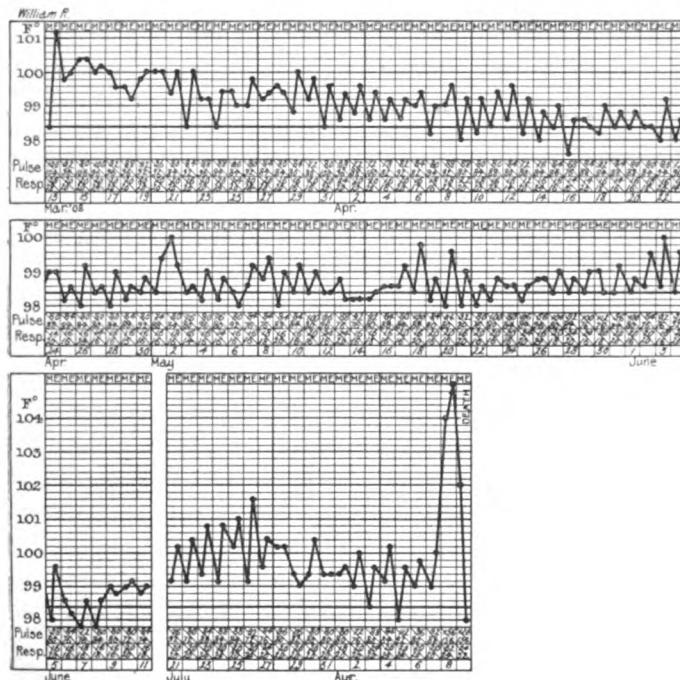
CASE 66.—Ref. No., Vol. 213, No. 151; Post-mortem, 1908.—Harriet B., æt. 41, was admitted under Dr. Hertz on March 13th, 1908, and died March 21st, 1908. She had been suffering from indigestion for over ten years, and from time to time had had much pain across her abdomen, accompanied by distension. Six years before her admission she had false teeth supplied, and her indigestion got much better. She has had ten children. She was admitted in the first instance into Dorcas Ward for ulceration of the mouth and necrosis of the lower jaw, the history being that after having a tooth extracted a few days previously, her jaw swelled to a great size, and for two nights the patient had been unable to sleep owing to the severity of the pain in the left side of her mouth. The gum was necrotic and ulcerated where the tooth was extracted. Only a few teeth remained, and the condition of all these was very bad. Owing to pyrexia and bruits it was thought that the patient had infective endocarditis, and she was removed to the medical wards. The temperature chart showed marked evening pyrexia. The pulse rate varied from 104 to 160, and the respiration rate from 24 to 52. The woman was exceedingly pale, with dark lines under her eyes. She looked sleepy, but her mind was clear, and she answered questions well. The heart was of normal size, and there was a widely-spread systolic bruit, probably of a hæmic nature. The lungs were natural. The alimentary system seemed natural, except for the state of the mouth. Neither the liver nor the spleen could be felt. The nervous reflexes were natural. The patient developed acute pleurisy, and gradually sank and died of exhaustion. At the post-mortem examination recent pleurisy was found over the right lung, and both lungs were pale and œdematous. The heart weighed 154 grams, and showed neither endocarditis nor pericarditis; but the myocardium exhibited typical tabby-cat striation. The liver was a typical café-au-lait colour, weighed 1,892 grams, and gave a very well-marked Prussian-blue reaction. The kidneys weighed 342 grams together, and the spleen weighed 146 grams. The blood count was as follows:—

Date.	Red corpuscles per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	White corpuscles per cub. mm.
13 March, 1908	—	20	—	2,000

Note.—Films showed marked poikilocytosis and megalocytosis. The number of red corpuscles is not recorded. Some blood was taken for culture, but no organisms were obtained from it.

The temperature chart was as follows:—
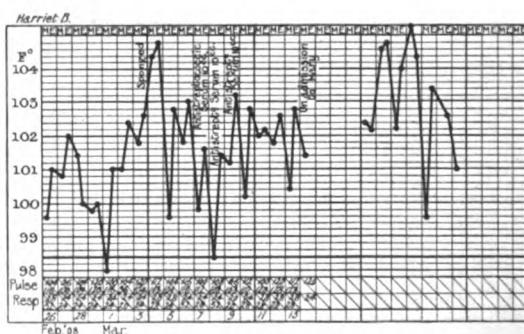
CASE 67.—Ref. No., Vol. 213, No. 19.—William C., æt. 34, a coal porter, was admitted for abdominal pains and anæmia under Dr. Shaw on September 30th, 1907, and was discharged relieved upon March 25th, 1908. Up to a year before his admission the only illness he had had was influenza, nine years before. He had been married for eight years and had three healthy children. He had lived at Gravesend all his life. His bowels were regular, and although he had never had a great appetite, he had had no gastric symptoms. The present illness began a year ago, when he felt generally unwell, and then began to lose his good colour and get short of breath. In December, 1906, he had to give up his work. Then he had pains in his abdomen, head and arms, and was short of breath. He stayed in bed under medical treatment for three months. Feeling a little better after this, he went to Eastbourne to a convalescent home for three weeks, and this made him much better. He went back to work on May 14th, 1907. Three weeks before admission he had a similar attack again with pains in his abdomen, head and arms. There was no bleeding anywhere. He simply became progressively weaker and anæmic. He was a fairly well-built man, by no means thin. The skin was the typical lemon-yellow colour, the sclerotics nearly white. The heart was perhaps slightly dilated, and there were hæmic systolic bruits in all areas. The lungs were natural. The spleen could be felt two inches below the costal margin. The liver could not be felt. The teeth were discoloured, many were carious, and there was much pyorrhœa alveolaris, though the mouth was otherwise clean. The ordinary nervous reflexes were natural. The urine had a specific gravity of 1020, was acid in reaction, contained no albumin, pus or sugar, but enough urobilin to be easily detected by the spectroscope. Arsenical treatment was adopted, but the condition of the abdomen made it difficult to continue with; nevertheless, there were times when he was able to take up to seven minims three times a day. No retinal hæmorrhages were present. In the course of treatment numerous pigmented spots developed on various parts of the body and limbs. The temperature chart showed various degrees of pyrexia. As improvement set in, temperature became normal, the pulse rate 70, respiration about 20.

The blood counts were as follows :—

Date.	Red corpuscles per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes, per cub. mm.
4 Oct., 1907	1,800,000	36	49	1·361	—
21 Nov., „	1,000,000	20	45	2·250	4,000
28 „ „	1,500,000	30	37	1·233	3,750
4 Dec., „	1,480,000	29	35	1·207	2,400
11 „ „	1,835,000	31	34	1·097	—
18 „ „	1,895,000	38	34	0·894	6,400
8 January, 1908	1,440,000	29	30	1·034	3,600
6 February, „	2,800,000	56	60	1·071	—

Note.—On October 4th, 1907, the differential leucocyte count was as follows :—S. 43, L. 1, P. 46, E. 3, B. 0. In stained films countless poikilocytes and many megalocytes were seen.

The temperature chart was as follows :—
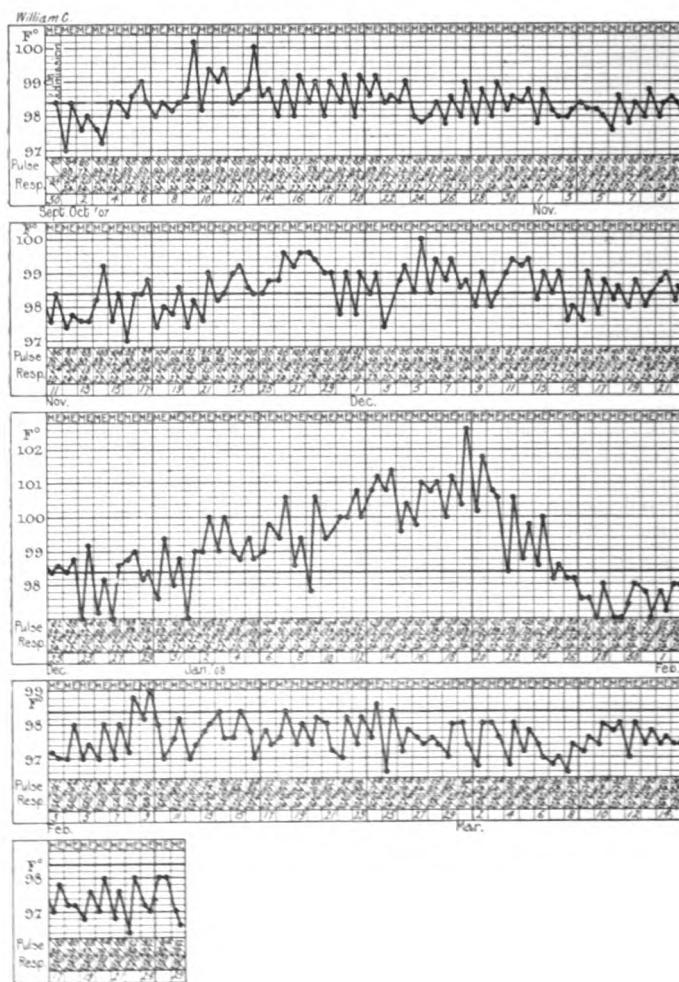
CASE 68.—Ref. No., Vol. 214, No. 237.—Alice I., æt. 28, a bar help, was admitted under the care of Dr. Hertz on April 14th, 1908, and was discharged relieved on May 9th, 1908. She has not been traced since. She gave the history that at 11 years of age she had had St. Vitus' dance, for which she was in Charing Cross Hospital; at 23 years of age she had had acute rheumatism, for which she was in St. George's Hospital ; at Christmas, 1904, she had what she was told was congestion of the liver, for which she was in Waterloo Hospital. She says she had a severe pain over the liver for which leeches were put on. When she was in the hospital she was told

that her liver and spleen were enlarged, and she was particularly asked if she drank much ; at Christmas, 1906, she again went to Waterloo Hospital complaining of dizziness, constipation, of a yellow-coloured skin, and of dark spots in front of her eyes. She was an in-patient. Pernicious anæmia was diagnosed, and she was relieved by the treatment she received. At Christmas, 1907, she was again in Waterloo Hospital for eight days, with the same symptoms, plus sickness. On the day after leaving Waterloo Hospital she went to St. Thomas's, where she remained five weeks. She was given medicine, which was probably arsenic, as it gave her diarrhœa, and made her eyes water. She was much relieved again. She left the hospital in February, 1908, and remained fairly well until the beginning of April, 1908, when she became ill again, and felt she was getting weaker and weaker every day. As before, she complained greatly of black spots before her eyes, severe headaches, and pain over her heart. Six days before admission she first noticed blood in her motions. She had never passed blood before, but she had suffered from " piles " for some time. She was a typical light-yellow colour, with a tendency to cyanosis. Her heart was of normal size with a suspicion of a local systolic bruit at the impulse, but no evidence of valvular disease. The lungs were natural. Great thirst was complained of, but the condition of the mouth was good, except for a furred tongue, but several teeth were decayed, and these were subsequently extracted under gas. The knee-jerks were unduly brisk, but otherwise the nervous system seemed natural. The urine had a specific gravity of 1015 ; it was alkaline, of a deep reddish colour, and contained no albumin or sugar, blood, urobilin, or indican. Analyses of the gastric juice showed absence of hydrochloric acid. The liver came down to the level of the umbilicus, and the spleen to one inch below that. The temperature was raised in the evening at first; as improvement set in it remained normal. The pulse rate varied from 70 to 100, and the respiration rate from 20 to 28. The patient was treated with cinnamon oil and liquor arsenicalis. She improved considerably in her general condition before she was discharged, though the blood counts do not indicate this clearly :—

Date.	Red corpuscles per cub. mm.	Red corpuscles, per cent. of normal.	Hæmoglobin, per cent. of normal.	Colour index.	Leucocytes, per cub. mm.
	Thoma Leitz.		Haldane.		Thoma Leitz.
14 April, 1908	1,200,000	24	26	1·083	7,500
20 ,, ,,	1,875,000	38	50	1·316	—

Note.—April 14th, 1908 : In stained films many poikilocytes, megalocytes, microcytes, and three nucleated red cells were seen.

The temperature chart was as follows :—
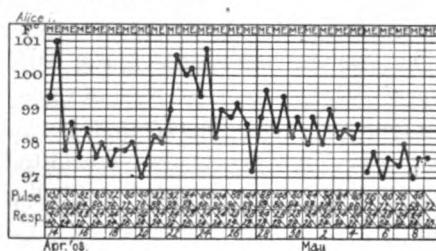
SUMMARY.

The following is a summary of the chief features of the above sixty-eight cases, as distinct from the "conclusions" on page 119:—

CHARACTERS OF THE URINE.

The urine in pernicious anæmia presents the very greatest variability both in colour, specific gravity, and constituents.

Blood.—It is noteworthy that blood was not recorded in a single specimen of urine in all the sixty-eight cases.

Albumin.—Albumin is seldom present in any large amount. It was found in eleven cases (Nos. 4, 7, 8, 11, 17, 24, 28, 33, 36, 37, 58), but seldom in more than a trace, and often only upon a single occasion.

Indican.—This is specifically mentioned as being present in excess in six cases (Nos. 7, 8, 10, 13, 28, 34), and as absent in four cases (Nos. 33, 48, 62, 68), whilst it is not mentioned at all in the remainder.

Urobilin.—This will be found at one time or another in almost every case of pernicious anæmia if it is tested for at intervals; if, however, it is looked for only on a single occasion, it is often recorded as absent. The test applied has been the ordinary spectroscopic one without any elaborate extractions. Making allowance for this, it is recorded as being found in twenty-three cases (Nos. 1, 7, 8, 9, 10, 13, 15, 16, 19, 21, 23, 25, 28, 29, 38, 43, 49, 52, 53, 57, 60, 62, 67), as not being found in twelve cases (Nos. 3, 11, 20, 22, 30, 38, 34, 35, 39, 45, 48, 68), whereas in the remaining thirty-three cases it is not mentioned at all.

Bile pigment.—Bile pigment was not obviously present in any case.

Sugar.—Glycosuria did not occur in any case.

Uric acid.—Spontaneous deposition of uric acid crystals, as a "cayenne pepper" precipitate that was obvious to the naked eye, occurred in four cases (Nos. 9, 11, 30, 37).

Reaction.—The reaction is nearly always acid to litmus paper; only in one case (No. 68) was it recorded as alkaline.

Tyrosine.—Seeing that the liver functions are very much altered from the normal in pernicious anæmia, it is not very surprising that, just as in acute yellow atrophy of the liver, leucin and tyrosine should sometimes escape being converted into urea and appear unaltered in the urine. In most cases it would probably be necessary to evaporate and extract the urine in order to detect the small amounts of tyrosine present, but occasionally the typical sheaves of crystals appear spontaneously in the deposit, as in case 52.

Colour.—The colour of the urine varies enormously in pernicious anæmia, both in different cases and in the same case at different times. The following notes are from successive cases about the time of their admission to hospital:—High coloured, pale sherry coloured, dark, light red colour, dark, constantly pale, dark, light coloured, high coloured, very pale, deep red-brown, pale amber, dark amber, abnormally dark, straw coloured, pale yellow, dark reddish, orange, dark, dark orange, dark brandy colour, pale yellow, dark, high coloured, amber yellow, pale, straw coloured, high coloured, pale and cloudy, amber, pale straw colour, reddish yellow, deep reddish. It is noteworthy that urobilin may be present even when the urine is pale, or at any rate not dark (*e.g.*, case 62).

Specific gravity.—As regards the specific gravity, the variations are equally great, yet well within the normal limits, as shown by the following figures from successive cases at or about the time of their admission to hospital:—1014, 1030, 1012, 1010, 1020, 1014, 1020, 1020, 1008, 1018, 1008, 1020, 1008, 1012, 1010, 1020, 1014, 1012, 1010, 1020, 1012, 1020, 1015, 1032, 1020, 1016, 1010, 1016, 1012, 1014, 1018, 1026, 1015, 1015, 1016, 1012, 1020, 1009, 1016, 1008, 1020, 1011, 1022, 1013, 1015, 1020, 1015.

ŒDEMA.

It is possible for extensive œdema to occur in pernicious anæmia, as in cases 3, 11, 30, 33, 35, 43, 51 and 65, where it involved not only the legs, but also the back and abdominal wall. It is much more common, however, for there to be no more than slight swelling of the feet and ankles when the patient is up and about, disappearing when he rests in bed, as in cases 2, 4, 6, 16,

18, 20, 23, 25, 28, 31, 36, 44, 46, 47, 53, 55, 57, 60, 64, or for there to be none at all, as in the remaining cases, some of which exhibited no œdema at all from start to finish.

SEROUS EFFUSIONS.

In some of the blood diseases it is common to find serous or inflammatory exudation into one or more of the serous cavities, either when the end is near, or earlier.   It is often taught that this is true of pernicious anæmia also, but to judge from the sixty-eight cases under discussion serous exudation or inflammations of serous membranes are the exception.   In fifty-six cases the serous membranes were unaffected, although in many of these the patient was followed to the post-mortem room. Only in the following were they affected :—

In case 6 there was ascites from " simple " peritonitis.
,,   10 there was acute terminal pericarditis.
,,   26 there was acute terminal pneumonia and pleurisy.
,,   28 there was a serous exudate of 1,200 c.c. in the right pleural
              cavity ; the left pleura was universally adherent.
,,   29 there was acute terminal pneumonia and pleurisy.
,,   35 there was ascites some time before death, the abdomen being
              incised and drained.
,,   43 there was acute pleurisy a little while before the end.
,,   53 there was pleurisy with effusion, requiring tapping twice.
,,   58 there was acute terminal pneumonia, pleurisy, pericarditis,
              and acute capsulitis of the spleen.
,,   63 there was acute terminal pericarditis.
,,   65 there was acute terminal pericarditis.
,,   66 there was acute terminal pleurisy.

Apart from quite terminal pneumonia, pleurisy or pericarditis, therefore, there were only four cases in which the term serous effusion could be used in its ordinary sense.

THE SIZE OF THE SPLEEN.

THE SIZE OF THE LIVER.

It is scarcely surprising that the liver should be enlarged in a disease in which the blood destruction appears to play so prominent a part.   Clinically the liver was not felt in thirty-six cases (Nos. 2, 4, 5, 9, 12, 13, 15, 16, 18, 19, 20, 21, 23, 26, 27, 28, 29, 32, 35, 36, 39, 40, 41, 42, 43, 45, 46, 47, 48, 50, 51, 54, 55, 57, 66, 67) ; it was " just palpable " in ten cases (Nos. 7, 8, 17, 24,

31, 44; 52, 56, 61, 64). It came about one inch below the ribs in twelve cases (Nos. 1, 3, 10, 14, 25, 33, 34, 37, 53, 59, 63, 65); two inches below the ribs in three cases (Nos. 22, 30, 62); three inches below the ribs in three cases (Nos. 6, 58, 60); four inches below the ribs in two cases (No. 11, 68). No mention of it is made in the remaining two cases. In confirmation of the clinical fact that the liver is so often palpable the weight of the organ post-mortem is more than normal in over half the cases. Thus :—

			Grams.					Grams.
In case	4	it was	...	1824	In case 30 it was		...	1312
„	11	„	...	2560	„	32	„	...	826*
„	17	„	...	1632	„	33	„	...	1390
„	22	„	...	2048	„	35	„	...	1128
„	25	„	...	1521	„	51	„	...	1848
„	26	„	...	2030	„	66	„	...	1892
„	28	„	...	1512			* A child of 10.		

THE PRUSSIAN BLUE REACTION.

In every case in which a post-mortem examination was made (cases 4, 10, 11, 13, 17, 22, 24, 25, 26, 28, 29, 30, 32, 33, 35, 37, 39, 40, 43, 48, 51, 53, 58, 61, 63, 65, 66), the Prussian blue reaction was well marked in the liver, and in nearly every case the viscus had the typical café-au-lait colour. As regards the corresponding reactions in the spleen and kidneys, they were noted as follows :—

Prussian blue iron reaction in the spleen.	Prussian blue iron reaction in the kidneys.
Case 10. Slight Fe reaction.	Case 10. Marked Fe reaction.
11. Good Fe reaction.	11. Marked Fe reaction.
17. Considerable Fe reaction.	17. Considerable Fe reaction.
25. No Fe reaction.	26. No Fe reaction.
37. Fair Fe reaction.	29. Some degree of Fe reaction.
39. No Fe reaction.	32. Considerable Fe reaction.
51. Marked Fe reaction.	35. Nearly as marked Fe reaction.
53. Some Fe reaction.	39. No Fe reaction, as of liver.
61. Good Fe reaction.	48. Quite as marked reaction, as in the liver.
63. Good Fe reaction.	51. Well-marked Fe reaction.
	53. Slight Fe reaction.
	61. Good Fe reaction.

ANALYSES FOR IRON.

In cases 33 and 35, analyses of the iron in certain of the viscera were made by Dr. J. H. Ryffel, who, in order to avoid the great

difficulties there are in washing the viscera clear of blood,
analysed organs from another case, not pernicious anæmia, at
the same time by precisely similar methods for purposes of
comparison   It was found that :—

> The control liver yielded 0·14 per cent. of Fe in the dried residue.
> The pernicious anæmia liver (case 33) yielded 0·34 per cent. of Fe in the
>   dried residue.
> The pernicious anæmia liver (case 35) yielded 1·015 per cent. of Fe in the
>   dried residue.
> The pernicious anæmia kidney (case 35) yielded 0·512 per cent. of Fe in
>   the dried residue.
> The pernicious anæmia spleen (case 35) yielded 0·335 per cent. of Fe in
>   the dried residue.

THE KIDNEY WEIGHTS IN PERNICIOUS ANÆMIA.

The kidneys are nearly always large and pale, and generally
they give a fairly good Prussian blue reaction (see pages 102 and
213).   The weights available in the above cases are as follows :—

In case	10	the weight of the two kidneys was	432 grams.
„	11	„	„	416
„	13	„	„	288
„	17	„	„	320
„	22	„	„	304
„	25	„	„	386
„	26	„	„	405
„	28	„	„	351
„	30	„	„	260
„	35	„	„	260
„	39	„	„	392
„	48	„	„	481
„	58	„	„	372
„	66	„	„	342

Doubtless part of the increased weight is due to the same
cause as that of an ordinary "india-rubber" cardiac kidney, but
owing to the anæmia there is pallor and not cyanosis.   There
were infarcts in cases 25 and 63 only.

THE HEART.

In the great majority of cases the heart is of natural size,
with its impulse at or near its normal position ; whilst when the
anæmia is profound there are hæmic systolic bruits in each
precordial area and in the veins of the neck, lessening in
intensity and even disappearing if the patient rallies and the
anæmia diminishes.   Post-mortem the muscle is pallid, with
well-marked tabby-cat striation, especially in the musculi

papillares of the left ventricle, whilst the valves are healthy ;
the pericardium is healthy except that there may or may not be
sub-pericardial petechiæ.

The only exceptions to the above rule amongst the sixty-eight
cases were the following :—

In case 10 there was terminal pericarditis.
    ,,   11 there was fungating endocarditis.
    ,,   22 the heart was large, weighing 14 oz.
    ,,   26 the heart was large, weighing 444 grams.
    ,,   46 the impulse was 1 in. outside the left nipple line.
    ,,   48 the heart was large, weighing 481 grams.
    ,,   58 the heart was very big, weighing 612 grams, the result of old
              mitral stenosis and recent aortic endocarditis and peri-
              carditis.
    ,,   63 there was terminal pericarditis.
    ,,   64 there was syphilitic aortic disease with regurgitation.

Bruit de galop.—A canter rhythm is so characteristic a physical
sign of pericarditis that one is a little too apt, perhaps, to forget
that it can also be produced by a dilated, particularly by a fatty
dilated, heart when there is no pericarditis at all. This is well
exemplified by cases 4 and 25, in which the bruit de galop was
well marked during life, whilst the absence of pericarditis was
confirmed by autopsy. It is possible, indeed probable, that the
canter rhythm in case 34 was of the same nature, but there was
no post-mortem examination to prove it in that case.

THE LUNGS.

It is remarkable how seldom there is anything the matter with
the lungs or pleuræ in pernicious anæmia, except agonal œdema ;
even a terminal pleurisy or pneumonia is distinctly uncommon.
Healed phthisis may, of course, be found in these as in any other
cases, and pleural adhesions of old date are to be expected.
Upon the whole, however, one may say that the lungs were
natural in sixty-one out of sixty-eight cases, being abnormal only
in the following :—

In case 17 there were rhonchi during life, but the lungs looked healthy
          post-mortem.
    ,,   26 there was acute terminal pneumonia.
    ,,   28 there was serous effusion with plastic pleurisy.
    ,,   29 there was acute septic pneumonia and pleurisy.
    ,,   53 there was acute pleurisy on both sides.
    ,,   58 there was acute terminal pneumonia and pleurisy.
    ,,   66 there was terminal pleurisy.

GASTRO-INTESTINAL SYMPTOMS.
See page 109.

THE MOUTH.
For the condition of the mouth and teeth see page 112.

HÆMORRHAGES.

There is no mention of any hæmorrhages in cases 5, 6, 15, 18, 19, 20, 21, 28*, 29*, 31, 32*, 35*, 36, 42, 47, 51*, 53*, 55, 56, 58*, 59, 64, 65*, 66*.

There was a specific mention that hæmorrhages were absent in cases 7, 33*, 45, 60, 67.

Retinal hæmorrhages were seen in sixteen cases (Nos. 2, 4*, 9, 10*, 11†*, 13*, 22*, 26†, 30*, 38, 39†*, 41†, 48*, 50, 57†, 63†*). They were looked for and not found in twenty cases (Nos. 1, 3†, 6, 7, 8†, 15*, 17*†, 18*, 20*, 23*†, 27*, 28*, 35*, 45*, 52, 53, 54*†, 60, 65, 67*).

Subcutaneous petechiæ or purpura occurred in twelve cases (Nos. 8, 11†*, 16, 23†, 24*, 25†*, 26†, 39†*, 40†*, 44†, 46*, 61†*.)

Blood was passed per anum, in small or large amounts, in twelve cases (Nos. 3, 11†*, 14†*, 17*, 23†, 34,† 37†*, 43, 44†, 54, 62, 68).

Epistaxis occurred in nine cases (Nos. 11†*, 25†*, 26† (extreme) ; 27 (severe) ; 37†*, 40†* (severe) ; 41†, 52, 57.

Hæmatemesis occurred in four cases (Nos. 34† (very slight) ; 40,†* 49 (doubtful) ; 63†*).

Hæmoptysis in three cases (Nos. 1, 12, 52†).

Bleeding gums in two cases (Nos. 26,† 34†).

Severe after tooth extraction in one case (No. 61†*).

Terminal cerebral in one case (No. 14†*).

It is clear that pernicious anæmia may prove fatal without at any time leading to serious hæmorrhage. It is also clear that small hæmorrhages, especially retinal and subcutaneous, are not infrequent in the later stages of the disease ; seldom, however, is the amount of hæmorrhage in itself serious, in only four out of sixty-eight cases (Nos. 11, 36, 40, and 61).

* The asterisk signifies that the patient died within a short time.
† The dagger signifies that there were also other hæmorrhages in this case.

It is noteworthy that even when much purpura and many retinal hæmorrhages have occurred, the prognosis, though often very bad, is not necessarily one of immediate fatality, as cases Nos. 38, 44, and 50 prove.

RETINAL CHANGES.

In addition to retinal hæmorrhages (for which see page 216), the following retinal changes were observed :—In case 4, choriditis and optic atrophy, possibly syphilitic ; in case 50, exudation around the optic discs ; whilst in case 65, although there was marked amblyopia, possibly due to tobacco rather than to pernicious anæmia, the optic discs looked natural.

SEX.

Of the sixty-eight cases, thirty-one were females and thirty-seven were males.

AGE.

Without distinction as to sex, the minimum age was 10 years;* the maximum age was 67 years ; and the average age of the whole sixty-eight cases was 45 years.

If we distinguish the ages according to sex, we find :—

MALES.			FEMALES.		
Minimum	...	22 years.	Minimum	...	10 years.*
Maximum	...	67 „	Maximum	...	55 „
Average	...	48 „	Average	...	43 „

If we work out the age-incidence by decades, we find that—

At 10	years of age	there was	1	case
Between 10—20	„	there were	0	
20—30	„	„	3	cases
30—40	„	„	11	
40—50	„	„	28	
50—60	„	„	19	
60—70	„	„	6	
70—80	„	„	0	

DURATION AFTER DIAGNOSIS.

INTERVAL BETWEEN FIRST SYMPTOMS AND CORRECT DIAGNOSIS.

* Case No. 32, *q.v.* There are points in which this case differs a little from other cases of pernicious anæmia.

RALLIES.

The number of times the patient rallied and improved in health was as follows:—

> Not once in twenty-one cases (Nos. 4, 6, 9, 10, 16, 17, 22, 24, 25, 26, 27, 29, 37, 48, 51, 56, 58, 59, 60, 63, 66).
>
> Once at least in nineteen cases (Nos. 2, 7, 12, 13, 18, 19, 20, 23, 31, 33, 35, 44, 45, 49, 50, 54, 58, 61, 65).
>
> Twice at least in sixteen cases (Nos. 3, 5, 11, 14, 21, 28, 30, 34, 38, 39, 41, 42, 47, 53, 62, 67).
>
> Three times at least in four cases (8, 32, 52, 68).
>
> Four times at least in one case (No. 57).
>
> Five times at least in three cases (Nos. 1, 15, 36).
>
> " Many times " in three cases (Nos. 43, 46, 64).
>
> Not known in one case (No. 40).

THE PATIENT'S WEIGHT.

It is a point in diagnosis that a pernicious anæmia case may keep up quite a good bulk even to the end. Emaciation, such as occurs in cancer cases, is possible in pernicious anæmia, but exceptional. At the same time there is nearly always loss of weight, sometimes considerable. This loss of weight, without great decrease in bulk, is due to the replacement of some of the heavier tissues by typical bright yellow fat.

The state of the body is not definitely described in twenty of the cases, but in the remainder the following notes were made:—

> Case 2. 140lbs.
> 3. Well covered.
> 5. An averagely plump man. Weight 10½st. without clothes.
> 6. A stout woman.
> 7. General flabby fatness rather than wasting.
> 8. Fairly well nourished and did not complain of loss of weight.
> 10. Loss of weight down to 8st. 9lb., but much less loss of bulk.
> 11. Little loss of bulk; weight 11st. 1lb. without clothes.
> 13. Height 5ft. 5in., weight 8st. without clothes.
> 14. 8st. 9lbs., increasing to 13st. 7lbs.
> 15. Not wasted, but thinner than he had been. Weight 10st. 5lbs. in clothes.
> 16. 9st. 11lbs. without clothes. Very slight loss of bulk.
> 17. Lost flesh slightly.
> 18. 130lbs. Has lost weight, but not bulk.
> 19. Very thin. 5st. 4lbs.
> 21. 7st. 2lbs.
> 22. A stout-looking woman, not wasted.
> 27. Looked well nourished, but said he had lost 2st. in weight.

Case 28. Somewhat thin. Later wasted from peripheral neuritis.

30. Had lost much weight.

31. Had not lost bulk, but weighed only 123lbs.; rose to 132lbs. in a little over two weeks.

32. Very wasted.

34. Loss of weight.

35. Had lost weight, but not bulk.

36. No obvious wasting, though very ill.

37. Not emaciated, though very weak.

38. Lost in weight, but not obviously in bulk.

39. Very thin.

40. Complained of loss of weight. Weighed 8st. 13lbs. on admission and 9st. 5lbs. later. Had been 13st.

41. Well covered with fat all over.

42. Lost weight, but not bulk.

43. Not emaciated, but tall and spare.

44. 9st. 10lbs., rising to 10st. 2lbs.

45. Decidedly plump.

46. A well-nourished woman.

47. 11st. 11lbs. Did not look wasted.

48. Well nourished, though *in extremis*.

51. Not at all emaciated (post-mortem).

52. Well nourished.

54. Getting thinner, but still fat.

55. Well covered.

57. Progressive loss of weight.

58. Thin and weakly.

59. Well nourished.

60. Had lost weight.

61. Had not wasted at all.

62. Had lost weight considerably.

67. Well-built man, by no means thin.

NERVE SYMPTOMS IN PERNICIOUS ANÆMIA.

THROMBOSIS.

In only two cases was thrombosis noted during pernicious anæmia (Nos. 21 and 54). In each case the thrombosis was in the right leg, and in each case it was not a terminal complication, but a relatively early accident.

MENSTRUAL DISORDERS.

In former days there was confusion between the severe anæmias that might result from long-continued loss of blood and true pernicious anæmia. It is worthy of note that in not one of the present sixty-eight cases was there either metrorrhagia or

menorrhagia. In more than one there was amenorrhœa, and in case 21 leucorrhœa was troublesome. Otherwise the pelvic functions were conspicuously natural. Of the thirty-one female patients five were spinsters.

ARTHRITIS.

There are not a few observers who regard a septic condition of the mouth as a potent cause of rheumatoid arthritis. The condition of the mouth in pernicious anæmia cases is sufficiently often septic (see page 113) to make one expect that rheumatoid arthritis should be fairly common in these cases. It is note-worthy, therefore, that only in one case (No. 30) was there definite subacute rheumatoid arthritis, whilst in one other there was "troublesome stiffness of the knee-joints." In the remaining sixty-six cases no joint troubles attracted attention.

RIGORS.

It may be noted that, although there is no mention of any rigors in sixty-four out of the sixty-eight cases, in four these were very definite symptoms, and in three of the four appeared to be directly connected with the disease.

In case 11 the rigors were terminal, and definitely associated with fungating endocarditis ; in case 39 "cold shivers" were an early symptom ; in case 50 the disease started almost suddenly with "a cold shiver" which made the patient so ill that he had to take to bed at once ; whilst in case 64, although the "attack of the shivers" that ushered in the illness three years before his admission might possibly have been malarial, it is noteworthy that each relapse was also associated with a similar attack of the shivers, leading, without perceptible interruption, directly into undoubted pernicious anæmia.

TENDERNESS OF THE LONG BONES.

It is well known that the shafts of the long bones are apt to be very tender in more than one of the blood diseases. Unfortunately the notes upon this point here are very incom-plete, the only actual statements available being as follows :—

Case 4. No tenderness of bone.
    7. Tenderness along all the long bones.
   25. No tenderness of bones.

Case 31. Long bones decidedly tender.
　　34. Tender long bone shafts.
　　35. Tender bones.
　　44. Bones of legs very tender.
　　52. Very tender bones.

THE BONE MARROW OF THE SHAFT OF THE FEMUR.

The tenderness of the long bones is thought to be associated with the changes in the marrow; it seldom happens that the femur marrow in a fatal case of pernicious anæmia is not dark red instead of yellow—" like red-currant jelly," as a rule—as in cases 10, 29, 30, 33, 39, 53, 58, 61, 63, and 65. This redness is, of course, by no means specific, for it occurs in a large number of different conditions in which there is profound anæmia and a severe strain upon the blood-forming organs. It is very constant in pernicious anæmia, and microscopically there is little or none of the usual fat left, its place being occupied by crowds of nucleated red corpuscles in every stage of formation, together with varying numbers of bone-marrow cells and leucocytes.

THE COLOUR INDEX.

The question of the colour index, and of the fact that it is quite often less than one in pernicious anæmia cases, is discussed on page 114. Analysis of the various blood counts, exclusive of cases where only one blood count was made, shows that—

In case 1 out of 27 counts the colour index was not greater than 13 mm.

„	2	„	4	„	„	„	0
„	3	„	10	„	„	„	1
„	7	„	5	„	„	„	4
„	8	„	13	„	„	„	4
„	9	„	3	„	„	„	2
„	10	„	22	„	„	„	17
„	11	„	13	„	„	„	6
„	13	„	4	„	„	„	3
„	14	„	3	„	„	„	1
„	15	„	8	„	„	„	4
„	16	„	5	„	„	„	2
„	18	„	10	„	„	„	5
„	19	„	5	„	„	„	3
„	20	„	5	„	„	„	4
„	21	„	2	„	„	„	1
„	23	„	5	„	„	„	2
„	25	„	5	„	„	„	3
„	27	„	17	„	„	„	12

In case 28 out of 11 counts the colour index was not greater than 3 mm.

Case	counts				index
,, 30	,, 10	,,	,,	,	3
,, 31	,, 2	,,	,,	,,	1
,, 33	,, 15	,,	,,	,,	8
,, 34	,, 12	,,	,,	,,	0
,, 35	,, 8	,,	,,	,	1
,, 36	,, 6	,,	,,	,,	5
,, 37	,, 3	,,	,,	,,	2
,, 38	,, 7	,,	,,	,,	3
,, 39	,, 6	,,	,,	,,	4
,, 41	,, 5	,,	,,	,	2
,, 42	,, 3	,,	,,	,,	0
,, 43	,, 21	,,	,,	,,	10
,, 44	,, 5	,,	,,	,	3
,, 45	,, 5	,,	,,	,,	3
,, 46	,, 3	,,	,,	,,	0
,, 47	,, 7	,,	,,	,,	3
,, 48	,, 3	,,	,,	,,	0
,, 49	,, 3	,,	,,	,,	2
,, 50	,, 2	,,	,,	,	2
,, 51	,, 4	,,	,,	,,	1
,, 52	,, 14	,,	,,	,,	1
,, 53	,, 12	,,	,,	,,	6
,, 54	,, 3	,,	,,	,,	0
,, 55	,, 4	,,	,,	,,	2
,, 56	,, 7	,,	,,	,,	2
,, 57	,, 19	,,	,,	,,	5
,, 60	,, 2	,,	,,	,,	0
,, 62	,, 4	,,	,,	,,	1
,, 64	,, 4	,,	,,	,,	0
,, 65	,, 5	,,	,,	,,	1
,, 67	,, 8	,,	,,	,,	1
,, 68	,, 2	,,	,,	,,	0

Out of a total of 391 counts the index was not greater than 1 in   162

THE SKIN.

The colour of the skin was typical lemon-yellow in almost all the cases by the time they were admitted to hospital; but it is most important to bear in mind that this yellowness is by no means the earliest symptom, as a rule.   Not a few cases had been definitely ill for months or even for years before the yellowness of the skin attracted attention.

The familiar mistaking of the colour for "jaundice" by the patient's friends is easily to be avoided if the pearly-white colour of the conjunctivæ is noticed.   In not one of the sixty-eight cases was there jaundice.

The yellow colour of the skin is very largely due to the skin itself becoming so thin as to transmit the colour of the underlying fat. The bright yellowness of the latter post-mortem in pernicious anæmia is almost characteristic.

The question of purpura is noticed on page 216.

As regards undue pigmentation of the skin, especially the freckle-like form, it was present in twelve cases (Nos. 15, 16, 23, 30, 43, 46, 48, 49, 53, 56, 65, and 67).

Pigmentation in the mouth (cases 43 and 53) is referred to on page 103.

The Malar Flush.

Attention may be drawn to the very noticeable appearance of some cases of pernicious anæmia, particularly when improvement has been considerable; and that is the persistence of a more or less yellow colour over the greater part of the face, with a warmer red flush over the malar bones and central parts of the cheeks. The colour is decidedly reminiscent of sunburn, and at first sight it suggests extremely good health; needless to say, this appearance is entirely deceptive. I think some cases may be recognised in the earlier stages of the malady before the malar flush has faded into the ultimate lemon yellow. The warmth of malar colour was presented very decidedly by cases 10, 14 and 45; whilst a near approach to it is given by the ward clerk's description of case 33 as " a pale woman with some colour in her cheeks."

SOME OBSERVATIONS ON PRIMARY CARCINOMA OF THE LIVER, WITH REFERENCES TO MUSEUM SPECIMENS.

By

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(From the Pathological Department.)

AN examination of the post-mortem records of Guy's Hospital for ten years (1897–1906 inclusive) gave an apparent total of 15 cases of primary carcinoma of the liver out of 5,233 autopsies. On further investigation these could be divided up as follows :—

(a.) Where growth was present in *more than one* other organ :—

    1. P.M. 389, 1902. In heart and kidney.

    2. P.M. 440, 1903. Carcinomatous infiltration of cervi cal glands, pleura, spleen, and kidneys.

    3. P.M. 144, 1904. Involvement of stomach, omentum, peritoneum, lungs and pleura. (Specimen 04/23. Curator's Room.)

    4. P.M. 531, 1904. Glands in right iliac fossa, and a mass surrounding cæcum. Mass in prostate (said to be a fibro-adenoma).

    5. P.M. 268, 1905. Growth in uterus, peritoneum, retro-peritoneal glands, pancreas and supraclavicular gland.

(b.) Where growth was present in *one* other organ, or glands only involved :—

    1. P.M. 162, 1898. In right lung. (Specimen 98/29. Curator's Room.)

    2. P.M. 246, 1902. Glands in portal fissure involved. (Specimen 02/25. Curator's Room.)

    3. P.M. 523, 1902. Glands in portal fissure involved. (Specimen 02/47. Curator's Room.)

    4. P.M. 251, 1903. Glands near pancreas involved. (Specimen 03/38. Curator's Room.)

    5. P.M. 408, 1903. In fourth dorsal vertebra. (Dr. Nicholson's slides.)

(c.) Where no growth could be found elsewhere :—

    1. P.M. 397, 1897. No specimen or slides available.

    2. P.M. 64, 1897.   ″   ″   ″

    3. P.M. 297, 1900. (Slide from post-mortem inspection.)

    4. P.M. 61, 1905. (Specimen 05/11. Curator's Room.)

    5. P.M. 527, 1905. (Dr. Nicholson's slide.)

In group (a) it seemed unlikely that any of these could be primary growths in the liver. A specimen of the liver from P.M. 144, 1904, was preserved in the museum. Microscopically the growth was secondary to growth elsewhere, probably breast. No material could be obtained of the remaining livers in this group, and they have, therefore, also been excluded.

In group (b) specimens or slides were available of all, and four out of the five were definitely primary carcinomata. The fifth case (P.M. 251, 1903) was secondary to growth elsewhere, in all probability prostate.

In group (c) two cases (P.M. 64 and P.M. 397, 1897) have been rejected, no slides or specimens being available. In another instance (P.M. 297, 1900), although no growth was found in any other organ, microscopically the growth in the liver is obviously not of hepatic origin. The two remaining cases are genuine instances of primary carcinoma.

The cases which are microscopically those of primary carcinoma are the following :—

1. P.M. 162, 1898. (Specimen 98/29. Curator's Room.)
2. P.M. 246, 1902. („ 02/25. „ „)
3. P.M. 523, 1902. („ 02/47. „ „)
4. P.M. 61, 1905. („ 05/11. „ „)
5. P.M. 527, 1905. (Dr. Nicholson's slides.)
6. P.M. 408, 1903. („ „)

It is obvious from the results obtained by the above analysis that a very careful microscopic examination is necessary before any case can be considered to be one of primary hepatic cancer. The apparent absence of growth elsewhere is no absolute guide. Growth may be latent in other organs and yet give rise to secondary deposits in the liver. This possibly is the explanation of the case in group (b.), P.M. 251, 1903, where the only other growth found was in glands near the head of the pancreas, and microscopically the liver tumour was of extraneous origin. Again in group (c.), P.M. 297, 1900, the only growth that could be found in this instance was in the liver, and microscopically it obviously had its origin elsewhere. Cases have been recorded where prostate has been normal to the naked eye, and yet microscopic examination was able to demonstrate the presence of malignant disease. The same is true of breasts and other glandular structures. The possibility of cancer having been present in an appendix removed during life should also be borne in mind.

During the same period (1897—1906) there were 144 instances of secondary cancerous deposits in the liver, the numerical ratio between primary and secondary hepatic cancer thus being 1 to 21 nearly. Secondary cancer is stated to be much more common in women than men, owing to the great frequency of uterine and mammary cancer in females. An analysis of the 144 cases does not confirm this statement, as seventy-seven of the cases occurred in men and sixty-seven in women. The uterus and ovaries contributed seven and the female mammary glands five cases. It is probable that the explanation of this difference is that very few of the patients with breast cancer and

cancer of the female pelvic organs die in hospital. It may be that secondary deposits in the liver from these organs are not so common as they are generally believed to be. Another suggestion is that malignant disease is increasing in men. Out of 100 cases of secondary deposits, collected from the post-mortem records of St. George's Hospital for ten years (1892—1902), sixty-six were males and thirty-four females.[1]

Age and sex.—Primary hepatic cancer can occur at any age, although the usual time for it to appear is between the ages of 40 and 60 years. It is more often found in males than females; four out of the six cases occurred in the former. The ages of these patients were sixty-two, sixty-five, sixty-seven and thirteen years. The remaining two were in females, whose ages were thirty-two and sixty-two respectively.

Although primarily a disease of adult life, it occasionally occurs in children. An interesting series of primary malignant growths of the liver in children under fifteen years of age was published in 1897.[3] There were twenty-nine cases collected from the literature. Eleven of these were carcinomata, the remainder being sarcomata. The ages ranged from eight weeks to fourteen years. Recently two cases occurring in infants of seven and nine months have been recorded.[4]

<div align="center">CLINICAL CHARACTERS.</div>

The six cases present a few points of clinical interest :—

Onset and early symptoms.—The onset was usually insidious, and marked by increasing gastric disturbance in four of the cases, where there was a definite alcoholic history. The earliest symptoms here were nausea on waking in the morning, accompanied in one instance by actual vomiting. Loss of appetite and inability to take solid food quickly followed. In one instance the gastric trouble was preceded by an increasing dislike of fat. Hæmatemesis and epistaxis occurred early in one case. The remaining two cases (case 1 and case 6) are clinically of exceptional interest. In one, the boy of thirteen years, no symptoms were present beyond slight drowsiness and an enlarging abdomen. He was admitted into Addison Ward, under Dr. Taylor, in April,

1898. Fourteen days before admission he was apparently quite well, and attending school. He then complained of his trousers being tight. It was noticed that his abdomen was unduly large. He seemed quite well otherwise beyond a slight drowsiness. The swelling increased, and he was brought to the hospital. There was a total absence of pain or discomfort. His condition on admission was as follows:—The abdomen was enlarged, measuring 27½ inches in circumference at the umbilicus. The abdominal wall was not tense, but there was some tenderness to the right of the umbilicus. A huge mass could be felt, which appeared to be the liver, on the right side reaching to the level of the anterior superior spine of the ilium. The surface of this mass was smooth ; a slight protuberance was evident near the umbilicus. There were distended veins over the whole abdominal region. The pulse was rapid, being 125 per minute.

Progress of the case.— April 1st. On admission, there was some vomiting. An exploring needle was used to see if there was any ascites, but only a few drops of blood were obtained. A diagnosis of "sarcoma of the liver; possibly hydatid," was made. On April 2nd, a broad band of pigmentation appeared on the left side, which increased, and on the following day extended partly over to the right side of the abdomen. Slight œdema of the abdominal wall was noticed. On April 4th, patient was sick again ; the pigmentation was well marked now on the right side. The veins of the chest wall were greatly swollen. The mass was again explored with a trochar and cannula, and again only a few drops of blood obtained. Pain was noticed for the first time on the 21st April accompanied by dyspnœa. The physical signs in the chest were normal. The patient became very much jaundiced, and the pain became very severe, necessitating the administration of morphia. Death took place on the 25th April.

This case illustrates the extreme rapidity of the disease, and also death from an unusual cause.[5] At the post-mortem death was found to be due to hæmorrhage into the peritoneal cavity.

In the remaining case, that of a man of sixty-seven, the initial symptom complained of was pain between the scapulæ, followed

later by paraplegia. Throughout the illness there were no symptoms suggestive of hepatic disease, although the paraplegia was due to a secondary deposit in the vertebræ, arising from a primary growth in the liver.

Pain.—Pain was not a marked feature in the early stages of the disease. It was rather a feeling of uneasiness and discomfort below the costal margin than actual pain. Pain in all the cases became severe towards the end.

Jaundice.—Jaundice was present in five out of the six cases. In three instances it occurred early, but was never very marked. In the other three cases it was late in onset, and in one instance only occurred three days before death.

Ascites.—Ascites was present in four instances, and occurred in the cases with a definite alcoholic history. Paracentesis was necessary. The fluid drawn off was pale yellow or orange in colour, alkaline or neutral in reaction. The specific gravity varied from 1010–1016. Albumen, chlorides, and traces of urea were present.

Urine.--The urine in five cases was darker in colour than normal. The amount passed varied with the presence or absence of ascites. The specific gravity ranged from 1020–1035. The reaction was acid, and a large amount of urates was present. The excessive quantity of urates is said to be a marked feature in hepatic cancer. The amount of urea increased in the early stage of the disease, being as much as 4·5 %, while towards the end it only amounted to 1·5 % or less. Bile pigment was present where jaundice occurred. Albumen was only present once.

Fæces.—The fæces were normal in colour in four cases. In the remaining two instances they were described as light yellow in one and clay-coloured in the other.

Temperature and pulse.—In one case the temperature was normal, or a little above, throughout, rising on two occasions to 100°. In three instances it was subnormal. In another the temperature was normal, with three exceptions, when it rose to 102°, 104°, and 101°. In the remaining instance, periods of pyrexia and apyrexia were present. In this case a rigor occurred once.

Pyrexia may be present in uncomplicated malignant disease. Usually the rise of temperature is not great. In some instances a peculiar tendency towards alternations of periods of pyrexia and apyrexia has been observed.[6]

Pulse.—The pulse was rapid in four cases, in one of which it averaged 125 beats per minute. In three it averaged 104 beats per minute. In the remaining two instances it varied between 80 and 90 beats per minute.

Prognosis.—From the onset of the earliest symptom until death the average duration of the disease was three and a half months. One patient lasted eight months. She was a woman (case 4), admitted as cirrhosis, who improved considerably, went out, and remained at home for three weeks; came back, again went out, finally returning to die. In the boy the disease was fatal in five weeks from onset. In the remaining cases death ended the scene in $3\frac{1}{4}$, 3, $2\frac{1}{2}$, and $2\frac{1}{4}$ months respectively. Five weeks was generally the duration of the illness from the time these patients were bad enough to remain in bed.

Diagnosis.—Mellanby has recently made an interesting discovery which may prove of considerable value in diagnosing malignant disease of the liver. It is that patients suffering from *cancer* of the liver excrete a considerable amount of creatin, a substance which normally does not appear in the urine. In *cirrhosis* and *engorged livers* creatin is *not* excreted, but the normal amount of creatinin is diminished.[7]

PATHOLOGY AND MORBID ANATOMY.

Origin of the new growth.—Cancer arising primarily within the liver may spring from any one of the following sources :—

1. Liver cells.
2. Bile ducts.
3. Suprarenal tissue and possibly "rests" of other organs.

Primary cancer in the majority of cases takes origin from the liver cells. More rarely it originates from the cubical epithelium of the small or columnar epithelium of the larger intra-hepatic ducts. The growth tends to spread rapidly, invading and compressing the normal tissue which in places

remains as mere strands.   Occasionally growth spreading in spaces formed by the atrophy and necrosis of normal cells appears to be encapsuled.   This apparent capsule is formed of flattened liver cells.   At the margins of the growth many atypical multinucleated cells can often be seen.   Various interpretations have been given in explanation of this phenomenon, which in all probability represents the final stage of the disappearing liver cells.   The continuity between the normal cells and those of the neoplasm can in many instances be made out by careful microscopic examination.   The resemblance to liver cells is not always found in these primary growths, as occasionally a reversion to the embryonic type of cells takes place.   In other cases growth arises from tissue of other organs, such as pancreas or suprarenal, included in the liver.   It has been stated to be not uncommon to find suprarenal tissue.   In the kidney the somewhat familiar " adrenal rest " tumour is sometimes found, and one case is on record where a similar " rest " in the liver gave rise to malignant disease.   Primary carcinoma from the intra-hepatic bile ducts is extremely rare.

The relation of cirrhosis to cancer.—The question of cancer arising in a cirrhotic liver is an extremely interesting one.   Three theories have been held at various times :—

    1.   That cirrhosis and cancer both develop together.
    2.   That cancer is the primary change.
    3.   That cirrhosis develops first.[1]

The last is the generally accepted theory, and recent work tends to show that cirrhosis is indirectly responsible for the malignant change in the liver cells.   Experimentally it has been demonstrated that excision of a large portion of the liver in animals is followed by more or less complete renewal within a short period.   The same phenomenon has been observed, but to a lesser extent, in man.   A very good example was found in the case of a man whose liver had been lacerated in an accident.[5]   He died, seventeen days after the injury, from empyema.   At the post-mortem blood-clot was seen filling up the spaces caused by the injury.   Microscopically it was shown that at the margins, and running into the blood-clot, there were columns of new liver cells,

together with connective tissue elements. In the one case the process is a simple compensatory hypertrophy, while in the other it is a direct attempt at repair by means of connective tissue and *proliferation* of cells. This power of regeneration by the liver cells is present at all ages, though naturally the younger the individual the more likely it is to take place. If this proliferation of cells continues beyond a certain point it becomes abnormal, and the starting place of malignancy. In certain morbid conditions of the liver, *e.g.*, cirrhosis, acute yellow atrophy, and atrophy resulting from venous back pressure, atypical masses of cells occur. These represent efforts on the part of the liver to repair and replace damaged tissue. These areas of atypical parenchyma have been termed " regeneration nodules."[9] The cells do not form columns radiating from a central vein, but are arranged in a somewhat concentric manner. The intra-lobular and portal veins are few. From this stage the "regeneration nodules" go on to that known as "regeneration adenomata." The cells here are smaller ; their growth is rapid, producing pressure effects on the surrounding tissue. There is very little trabecular arrangement, and very few capillary spaces. This stage merges into that of the "malignant adenoma," which consists of broad masses of cells lying in lymphatic and vascular spaces. These cells are arranged in columns separated by capillaries, and, finally, invade the liver in all directions.

The earlier changes can be seen in a large number of cirrhotic livers. The question then arises, why is it, since cirrhosis is so frequently met with, there are so few cases of cancer arising from this source? The answer most probably is that these atypical cell-masses become strangled and atrophy in the majority of these diseased livers. Microscope slides from case 3 show very clearly the changes immediately preceding carcinoma in a cirrhotic liver. In one slide "regeneration nodules" and " regeneration adenomata " are present, but there is no evidence of malignancy. Other slides from the same case show quite well the presence of new growth invading the vessels and producing compression effects. In almost every case of hepatic carcinoma, whether primary or secondary, the portal and hepatic veins

become filled with malignant thrombi. Thrombosis of these veins is a feature which does not appear to be generally recognized. Closely connected with the presence of malignant thrombi in the veins is the question of metastases. Secondary deposits from primary hepatic carcinoma do occur, but perhaps less frequently than from cancer elsewhere. They are carried by the blood stream, rarely by the lymphatics, and are found principally in lungs and pleura, and occasionally in bones (case 6).

CASE 1.—Primary carcinoma. (Curator's Room, Specimen 98/29. Inspection 162, 1898.)

H. R., æt. 13. Schoolboy. Admitted April 1st, 1898, under the care of Dr. Taylor. Died April 25th, 1898.

Clinical history.—This has been given above.

Summary of the autopsy, which was performed by Sir Cooper Perry.—The body was wasted ; the skin was jaundiced, of a light yellow colour. The lung bases were compressed. Petechial hæmorrhages were present beneath both layers of the pericardium. The heart was normal. There were adhesions between the intestines. A considerable quantity of blood of recent date was found in the peritoneal cavity. The testes and pelvic organs were not examined. The glands in the portal fissure were enlarged.

Liver, 163 ozs.—The anterior surface was adherent to the abdominal wall. The whole organ was enormously and uniformly enlarged. It was full of masses of bile-stained growth, the central parts of which showed caseation, while at the periphery of them some hæmorrhage was present. There was very little healthy tissue left. The origin of the growth was thought to be probably in the thicker part of the liver. The liver edge in parts was approximately normal.

Secondary deposits.—One small deposit of growth was found on the surface of the upper part of lower lobe of right lung.

Description of museum specimen.—A slice right through the liver, showing many large lobulated white nodules of new growth. Into many of these hæmorrhage has occurred. Between the large lobules there are some scattered nodules, varying in size from mere specks to a pin's point. The branches of the hepatic

vein present numerous nodules of new growth projecting into their lumen. Some branches are distended and blocked with new growth. In places the liver has a " nutmeg " appearance, and especially in the large nodules.

Histology.—Examination of slides shows :—

1. Growth invading normal tissue, causing compression and atrophy of liver cells, which in many places remain as mere strands with flattened nuclei.

2. Masses of large atypical multi-nucleated cells in the compression areas and bordering on the new growth, representing possibly attempts at regeneration on the part of the disappearing normal tissue.

3. The new growth is composed of cells having little resemblance to liver cells, and is advancing along spaces apparently formed by necrosis and atrophy of liver tissue. It is arranged in irregular columns, with spaces in them containing bile. The presence of bile is constant throughout the growth, and is suggestive of the hepatic origin of the neoplasm.

4. The growth resembles suprarenal tissue, but the presence of bile in it, and the continuity between its cells and those of the liver, which can be traced here and there, almost certainly prove its hepatic origin. It is probably a reversion to the embryonic type of liver cell.

5. The growth is breaking down in places, and hæmorrhage into it has occurred, with destruction of its cells.

CASE 2.—Cirrhosis and primary carcinoma. (Curator's Room, specimen 02/25. Inspection 246, 1902.)

Clinical history.—A. E., æt. 62, male. Admitted 25th May, 1902, under the care of Dr. Newton Pitt. Died 10th June, 1902. He came in for swelling of the abdomen and œdema of the legs. He had suffered from " bilious attacks " for years. There was a definite alcoholic history. There was a history of illness for three months before admission ; swelling of abdomen, slight jaundice and pain. After admission, bleeding from nose and gums occurred, and ascites increased. Paracentesis was performed. The patient gradually became weaker and died.

Summary of the autopsy, which was performed by Dr. Bryant.— The body was wasted, and markedly jaundiced. The legs were œdematous. Heart: The endocardium was deeply stained with bile, and the intima of the vessels was also bile-stained. Fluid was present in the peritoneal cavity.

Liver, 4,210 grammes.—This organ was very much enlarged, and the surface was irregular and nodular. The nodules were not very large. The whole liver was involved, and many small nodules projected from the surface. These were deep, almost olive-green in colour, and were soft and fluctuating. The superficial blood-vessels were dilated. The tissue between the nodules was pinkish-grey in colour. A large mass of yellowish growth, nearly the size of a billiard ball, was present on the under surface of the liver. It was situated about five cm. above the neck of the gall-bladder and extended into it. No growth could be found elsewhere in the body.

Description of museum specimen.—A portion of the liver of brownish appearance, in which there is a certain amount of cirrhosis between the lobules. The latter stand out well. The liver is studded all over with small green bile-stained nodules, the larger of which are necrotic in their centres. They average about ·5 cm. in diameter. Other larger and isolated nodules, whitish in colour, averaging 1·5 cm., can be seen. There is a small white nodule, apparently of new growth, projecting into a branch of the hepatic vein.

Histology :—

1. Considerable cirrhotic change in liver.
2. Masses of atypical cells showing clearly all the stages, from a "regeneration nodule" to a "malignant adenoma."
3. The continuity between the new growth and the liver cells can be made out.
4. Bile is present in the neoplasm.
5. The cells of the growth in places are arranged round spaces, and have the appearance of pancreas.

The slides from this case are particularly interesting in that they show how a primary carcinoma of the liver may simulate

other tissues. Thus, while an examination of one microscope slide shows a resemblance to pancreas, an examination of others proves it to be definitely of liver origin.

CASE 3.—Cirrhosis and primary carcinoma. (Curator's Room, Specimen 02/47. Inspection 523, 1902.)

Clinical history.—W. J., æt. 65. Stoker in brewery. Admitted 23rd October, 1902, under the care of Dr. Bryant. Died November 24th, 1902. He was admitted for ascites, and gave a definite alcoholic history. The first symptoms were noticed two months before his admission, and were those of early morning nausea and increasing size of abdomen. After admission the ascites increased and paracentesis was performed. The patient gradually became worse; vomiting and hæmatemesis occurred. He became slightly jaundiced towards the end, which rapidly followed on drowsiness and coma.

Summary of the autopsy, which was performed by Dr. Bryant.— The body was very emaciated. The skin was sallow and slightly jaundiced. Slight brown pigmentation of the face was noticeable. The veins at the lower end of the œsophagus were dilated.

Liver 2310 *grms.*—This organ was pale yellow in colour. Its surface was irregular and nodular, the nodules being small. In places projecting from the surface were a number of brownish-green soft nodules, some being about 2 cm. in diameter. The liver substance was harder than normal. Its edge was thick and irregular. On section, the organ was pale and apparently infiltrated with bands of fibrous tissue. There were streaks and patches due to fatty change.

Secondary deposits.—None. The glands in the portal fissure were enlarged. Sections were not cut of these. No growth could be found elsewhere.

Description of the museum specimem.— A sagittal section through the liver at its hilum. The upper half appears free from growth except for a few scattered white nodules in hepatic veins. Lobulation of this part of the organ is well marked, and to the naked eye shows no increase of fibrous tissue. The lower half of the liver is more fibrous and pale in appearance. It is almost entirely occupied by irregularly lobulated nodules of

new growth of varying size, from a pin's head to 2 cm. in diameter. The nodules are white or stained green with bile. The large branches of the hepatic vein at the hilum are entirely occupied and distended with white masses of new growth having hæmorrhage into them.

Histology. --

1. There is well-marked cirrhotic change in the liver, and the slides show extremely well " regeneration nodules " and " adenomata."

2. Typical glandular carcinoma arising from liver cells.

3. Section showing a vessel the walls of which are very much thickened. It contains within its lumen new growth.

CASE 4.—Cirrhosis and primary carcinoma. (Curator's Room, Specimen 05/11. Inspection 61, 1905.)

Clinical history.—E. M., æt. 32. Female. First admission, August 4th, 1904. Last admission, December 2nd, 1904. Death, February 6th, 1905. She was said to have been quite well until June, 1904, when she had an attack of hæmatemesis, followed by diarrhœa and vomiting. She recovered and remained well until August, when she again had attacks of vomiting. On August 4th she was admitted, under the care of Dr. Pitt, for hæmatemesis. She had slight jaundice then, but no ascites. She left the hospital on October 3rd, to be readmitted again three weeks later, under the care of Sir Cooper Perry. This time she had well-marked ascites. She went out again on November 4th, to be readmitted on December 2nd, under the care of Dr. Pitt. Ascites was then very marked, and paracentesis was performed on three occasions, fifty-four pints of fluid being removed in all. Severe diarrhœa set in, followed by coma two days before death, which occurred on February 6th, 1905. (This history is un- usually long for primary carcinoma, and suggests that the case, when first seen, was purely cirrhosis.)

Summary of autopsy, performed by Dr. Fawcett.—There was recent pleurisy over the right lung. The peritoneal cavity, which contained twenty pints of fluid, showed signs of recent peritonitis. The spleen, which was very large, weighed 620 grms.

Liver (weight not recorded).—This organ was much altered from the normal. In parts it showed well-marked cirrhosis, while other areas were occupied by deposits of soft growth stained a greenish-yellow colour with bile. The gall-bladder was normal.

Secondary deposits.—None.

Description of museum specimen.—A pale cirrhotic liver with a finely granular external surface. Some old adhesions and thickening of capsule can be seen. The cut surface is distinctly fibrous, and the liver lobulation exceedingly well-marked. This marking becomes more and more uniform near the upper part of the liver, so that the lobules merge into masses of new growth, between which are the fibrous bands. The upper part of the liver is entirely occupied by a mass of growth, necrotic in the centre. Some veins can be seen which are distended with new growth. The gall-bladder is slit open, and apparently is quite normal.

Histology.—Here again sections show " regeneration nodules and adenomata " in a cirrhotic liver, leading to typical hepatic carcinoma.

CASE 5.—Cirrhosis and primary carcinoma. (Dr. Nicholson's slides. Inspection 527, 1905.)

Clinical history.—E. F., æt. 62, Female. Admitted 11th October, 1905, under the care of Dr. Taylor. Died 29th October, 1905. She was admitted for swelling of the abdomen. She had a definite alcoholic history. There was a six weeks' history of illness before coming to the hospital. This illness began with loss of appetite followed by pain, vomiting, and enlarging abdomen. There was no bleeding from nose or gums. On admission patient was jaundiced, and had well-marked ascites. Paracentesis was performed. Patient became gradually weaker and died.

Summary of autopsy, performed by Dr. Bell-Walker.—The body was wasted and slightly jaundiced. The lung bases were œdematous. The heart muscle was pale, and the coronary arteries were slightly atheromatous. There were five pints of clear fluid in the peritoneal cavity.

Liver (weight not recorded). In shape and size this organ was practically normal. It was universally tough and hobnailed. The left lobe contained many circumscribed pale areas. Some of these were hard, and resembled new growth. Others were soft and breaking down; one especially, on the front of the left lobe, contained soft pultaceous material. There was no evidence of hæmorrhage into the breaking-down areas. No growth could be found elsewhere in the body.

Secondary deposits, none.

Histology.—An examination of microscopic slides showed :—

1. Well-marked cirrhotic liver.
2. " Regeneration " nodules, " adenomata " and malignant change.
3. Masses of multinucleated atypical cells.
4. Continuity of growth with liver cells.

CASE 6.—Primary carcinoma of liver, with a deposit in dorsal vertebræ. (Dr. Nicholson's slides. Inspection 408, 1903.)

(This is a case of unusual interest, which is described in the post-mortem records as one of sarcoma of the vertebræ.)

Clinical history.—J. E., æt. 67 (optician). Admitted 19th August, 1903, under the care of Dr. Taylor. Died 20th October, 1903. He was admitted into the hospital for paraplegia. For two months before admission he had had pain between the scapulæ. Three weeks before admission the left leg began to get weak, followed a week later by weakness of the right leg. After admission he suffered from incontinence of urine and fæces. He gradually got weaker and died. There were no symptoms recorded suggestive of liver disease. There was no jaundice or ascites. The urine appears to have been darker in colour than normal.

Summary of the autopsy, performed by Dr. Barber.—A soft vascular growth was found between the bodies of the third and fourth dorsal vertebræ, situated chiefly on the left side. There was a constriction of the spinal cord opposite this mass of new growth. The rest of the vertebral column and spinal cord appeared to be normal.

Liver (weight not recorded).—The liver was enlarged. A large round mass of new growth was seen on the upper part of the right lobe, about two inches in diameter.

Histology.—(Specimens of the liver were not kept, and the only available slides are those of Dr. Nicholson's.) The mass in the liver was a primary carcinoma of that organ, and that in the vertebræ was a secondary deposit consisting of typical hepatic cells.

CONCLUSIONS.

1. Primary carcinoma of the liver is extremely rare, being ·1 per cent. of all hospital cases.

2. The post-mortem finding of " no growth elsewhere " is not sufficient to justify a diagnosis of primary carcinoma in the liver. Latent growth in prostate, breasts, or other glandular structures may have given rise to the neoplasm.

3. The disease runs a very rapid course ; the average duration of the illness being three and a half months.

4. Cirrhosis is a predisposing cause of primary carcinoma. Four out of the six cases were examples of carcinoma following cirrhosis.

5. The new growth in these cirrhotic cases is due to an attempted regeneration on the part of the liver cells which, in the absence of a controlling influence, follow the course of malignant disease.

6. The cells of the new growth in some instances tend to simulate the arrangement of other glandular structures, *e.g.*, pancreas and suprarenal.

7. Bile occurs in the neoplasm in a few cases.

APPENDIX.

Analysis of 144 Cases of Secondary Carcinoma of the Liver collected from post-mortem reports of Guy's Hospital for ten years (1897–1906 inclusive).

Seat of primary growth.	Number of cases of secondary carcinoma in the liver.	Sex.		Total number of cases of carcinoma during same period.	Percentage of cases giving secondary deposits in liver.
		Male.	Female.		
Stomach	29	16	13	121	35·09
Œsophagus	17	13	4	79	21·5
Rectum	15	9	6	54	27·7
Colon	10	5	5	34	29·4
Sigmoid Flexure ...	11	8	3	35	31·4
Duodenum	5	3	2	8	62·5
Cæcum	2	1	1	10	20·0
Ileum	1	—	1	4	25·0
Pharynx	1	1	—	7	14·2
Gall bladder	12	—	12	22 }	58·3
Bile ducts	2	1	1	2 }	
Pancreas	13	7	6	29	44·8
Kidney	3	3	—	10	30·0
Prostate	3	3	—	6	50·0
Bronchus	3	3	—	11	27·3
Lung	1	—	1	4	25·0
Tongue	1	1	—	24	4·2
Lip	1	1	—	3	33·3
Testicle	1	1	—	2	50·0
Carcinoma of many organs (? origin) ...	1	1	—	—	—
Mammary gland (female) ...	5	—	5	21	23·8
Ovary	4	—	4	14	38·6
Uterus	3	—	3	19	15·8
Bladder	—	—	—	6	—
Larynx	—	—	—	6	—
Floor of mouth ...	—	—	—	3	—
Peritoneum and omentum	—	—	—	3	—
Suprarenal	—	—	—	2	—
Anus	—	—	—	2	—
Penis	—	—	—	2	—
Vulva	—	—	—	2	—
Tonsil	—	—	—	1	—
Scrotum	—	—	—	1	—
Antrum, Highmore's					
	144	77	67	549	—

All figures and statistics are more or less fallacious, and convey only a rough idea of the prevalence, mortality, etc., of malignant

disease. Figures obtained from a general hospital are certain to differ from those obtained from special hospitals. A comparison of some of the results obtained in the above table with those obtained by the Cancer Research Laboratories of the Middlesex Hospital is interesting. While our figures only include cases for a period of ten years, their record is of cases for forty-six years.[1]

The following is a comparison of the percentages of metastatic deposits in the liver from carcinoma in other organs.

		Guy's Hospital.		Middlesex Hospital.
Stomach	...	35·09	...	39·0
Œsophagus	...	21·5	...	31·0
Rectum	...	27·7	...	40·0
Colon	...	29·4	...	26 0
Prostate	...	50·0	...	43·0
Bladder	...	None.	...	9·0
Breast	...	23.8	...	47·0
Ovaries	...	38·6	...	24·5
Uterus	...	15·8	...	11·9

A point of interest here is the large proportion of secondary deposits given by the prostate as compared with those given by the bladder. There were six cases of carcinoma of the bladder in our series, of which none gave metastases. In the figures of the Middlesex Hospital there were thirty cases, and in only three instances were deposits found in the liver. The explanation possibly is that the liver is not a suitable place for bladder tissue to grow.

In conclusion, I wish to express my thanks to the physicians of Guy's Hospital for kindly allowing me to make use of the cases recorded in this paper ; also to Dr. Fawcett for permission to examine the specimens in the Curator's Room of the Museum, and to Dr. Boycott and Dr. Nicholson for their kind assistance.

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UNILATERAL EXOPHTHALMOS.

A STUDY IN OVER 300 CASES RECORDED AND UNRECORDED.

By

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THE condition known as exophthalmos—protrusion of the eyeball from the socket—is a very interesting one, partly owing to the great variety of the lesions which produce it, and partly owing to the serious risks to sight or life which these lesions may cause. The average position of the eyeball in the orbit is such that if a straight-edge be applied to the upper and the lower margin of the orbit in a vertical direction the cornea will just be posterior to it. This, however, cannot be taken as a fixed rule, and individuals vary much. The general condition with regard to the presence or absence of fat affects the position of the eyeball, corpulence causing a protrusion of the eyeballs and emaciation making them sink back into the orbits. The configuration of the face also affects the apparent position of the eyeballs, and so does the size of the globes themselves, highly myopic and buphthalmic eyes being apparently proptosed owing to their large size.

Owing to the frequent variations from the average position of the eyeball, the presence of slight bilatera exophthalmos is very difficult to determine, though greater degrees are obvious. When one eye only is affected the condition is much more easily detected in the early stages owing to the possibility of comparison

with the other eye. For this purpose it does not usually suffice to examine the patient from the front, for slight increase of the palpebral fissure from affections of the lids may produce the appearance of apparent exophthalmos. In the detection of slight unilateral proptosis of one eye the patient should be seated. The surgeon standing behind and looking down the patient's face from above directs him to gradually raise his eyes from the floor until the corneæ become visible. The relative position of each cornea to the upper orbital margin then denotes the presence or absence of exophthalmos, provided the eyes are of the same size. For the accurate estimation of the amount of the proptosis an instrument is used. Even then the determination may present difficulties owing to the eye sometimes being rotated in a direction other than horizontal in addition to being proptosed.

In severe degrees of exophthalmos the eyelids are unable to close completely over the globe, and ulceration of the cornea is produced, with consequent deterioration of sight. To combat this it may be necessary to sew the eyelids together after freshening their edges over the middle two-fourths.

This paper is founded mainly upon the cases in the wards of the Royal Eye Hospital, Southwark, during the last ten years, the Eye Wards at Guy's Hospital during a similar period, and the cases recorded in the Transactions of the Ophthalmological Society of the United Kingdom since its foundation in 1880. A few cases are taken from the Out-patient departments and other sources named in the list of references.

The experimental production of exophthalmos is a subject which has been much worked at by various observers. Edmunds[1]* summarises the methods which produce it:—

I. Stimulation of the cervical sympathetic.

II. Administration of drugs, *e.g.*, cocaine or thyroid extract. The action of cocaine is very temporary, whereas thyroid gland extract, given in large doses, produces an effect which lasts much longer, but gradually diminishing on diminution of the dose.

*The small numbers found throughout refer to the list of references at the end of the paper

The reverse of exophthalmos is produced by :—

I. Section of the sympathetic. In this class may possibly be put some cases of fracture of the bone around or through the optic foramen. One such case has come under my own care.

II. Removal of the thyroid gland in whole or part, or by ligature of its arterial supply. Removal of the parathyroids has, in some cases, produced exophthalmos; but generally no effect on the eyes follows their removal.

No further mention will be made of these methods of affecting the position of the eyeball.

CONGENITAL EXOPHTHALMOS.

Exophthalmos has been found at birth in the following conditions :—

I. Oxycephaly. A case of this malformation is at present under treatment at the Royal Eye Hospital, by Dr. Willoughby Lyle. Each eye is markedly proptosed, but while the child is quiet the proptosis is equal in amount. When the child cries, however, the right eye is suddenly shot forward so as to lie entirely outside the orbit, and the lids will not then close over it. Possibly in this orbit there is some defect in the bony wall, so that increased intracranial pressure is readily communicated to the region behind the eyeball, dislocating the latter entirely from the socket. Paton[2] describes the case of a female, æt. 31, whose eyes were markedly proptosed from this deformity, the right eye being completely blind. A more advanced case still was under Harman,[3] in which proptosis was so bad that the eyes appeared to be almost dropping out, and the child had to go about with a hood over its head to cover the deformity. The eyes were quite blind.

II. Anencephaly. Here the extent of the exophthalmos depends partly on whether the orbital plates of the frontal bones are present or not. Usually there is considerable proptosis, as is well shown in specimens in the Royal College of Surgeons Museum.

III. Microcephaly. A splendid specimen of this anomaly causing proptosis is in the museum at St. Bartholomew's

Hospital, and is referred to by Power.[4]   The orbits are extremely small, too small to receive the eyeballs at all.   A perpendicular line from the front of the vertical part of the frontal bone falls entirely behind the globes.   The eyelids could be drawn over the corneæ, and were fixed there by suture, so as to preserve the eyes during the child's life, which lasted thirty days.

IV.   Microphthalmos.   Cruise[5] records an interesting case of cyst of the orbit with microphthalmos and proptosis, in which the history was that a tumour had been present in the orbit from earliest infancy, although, as t had not been protruding through the lids, no treatment had been sought until the .age of twenty-one.   There was a free passage between the cyst and the interior of the globe, allowing the fluids secreted by the ciliary processes to pass into and distend the cyst and so cause its enlargement.

V.   Hydrocephalus rarely produces a condition of exophthalmos. More usually apparent enophthalmos is present owing to the projection forwards of the frontal bones by the increased intracranial pressure.

VI.   Pulsating exophthalmos.   This condition, much more often found in adult life, will be more fully described later.   Its congenital occurrence is very rare.   Clarke[6] records a case first seen by him at the age of three years, with considerable displacement down and out, in which the condition was noticed at birth.   A blowing murmur was heard over the temporal region, and the optic disc of that side was of a pearly whiteness.   There was no history of injury at birth or afterwards.   The child was alive and well at the time of the record.   Rockliffe[7] also describes a case seen at an earlier age of twenty-two months.   In this the displacement was downwards and inwards.   Under chloroform a tumour was felt in the back of the orbit.   The condition varied from time to time both as to pulsation and proptosis.

VII.   Congenital tumours.

1. Teratomata or teratoid tumours.   These rare forms of new growth contain connective, endothelial, and epithelial tissue, as if derived from all three layers of the embryo.   When affecting the head they are of very variable size.   Stannus[8] records one of such

dimensions that the eye simply formed part of a large protruding tumour, which on microscopical examination was found to consist of several varieties of tissue, and hence to belong to the above class.

2. Dermoids. Though these tumours are present at birth, I can find no record of their being of such a size as to cause proptosis of the eyeball at that time. Their presence later in life will be dealt with presently.

3. Meningocele. As a possible cause of congenital orbital tumour, meningocele has certainly to be borne in mind, though reported cases in which autopsy has confirmed the diagnosis are exceedingly rare. Guersant[9] showed an infant with this condition, at the Medical Society in Paris, in which at the autopsy the tumour was found to consist of a small portion of brain substance covered by the membranes of the brain, which had passed through the fronto-ethmoidal suture and appeared at the inner angle of the orbit.

In adults the conditions that cause exophthalmos may be classified in the following way :—

I. Primary intra-orbital.

II. Primary extra-orbital.

        (a) Extending into the orbit from adjacent cavities or sinuses.

        (b) Metastatic deposits.

With the exception of the last class these may be again divided as follows :—

I. Simple hypertrophy of orbital wall or some of its contents.

II. Inflammatory. *A.* Simple. *B.* Syphilitic. *C.* Tubercular.

III. Vascular.

        1. Hæmorrhage into the orbit.

        2. Intermittent vascular dilatations.

        3. Thrombosis of intra- or retro-orbital venous channels.

        4. Pulsating exophthalmos.

        5. Angioma.

        6. Lymphangioma.

IV. Cysts.

        1. Hæmorrhagic.

        2. Hydatid.

        3. Dermoid.

V. Solid Tumours.

    A. Innocent.

        1. Exostosis.

        2. Adenoma and fibro-adenoma.

        3. Myxoma.

        4. Lipoma.

        5. Neuroma.

        6. Plexiform neuroma.

        7. Lymphoma.

    B. Malignant.

      Primary.

        1. Sarcoma.

        2. Chloroma.

        3. Carcinoma.

        4. Endothelioma.

      Secondary.

        1. The same by extension.

        2. Carcinoma by metastasis.

Tumours of the optic nerve are of such interest that a separate class may be formed of these alone. They may be divided into intra-dural and extra-dural according to their exact origin, and into innocent and malignant according to their nature. Of these the following have been described :—

      Innocent.

        1. Fibroma.

        2. Myxofibroma.

        3. Psammoma.

        4. Cysts.

      Malignant.

        1. Glioma.

        2. Glio-sarcoma.

        3. Sarcoma.

        4. Metastatic sarcoma and carcinoma.

  VI. Traumatic exophthalmos.

  VII. Exophthalmos associated with cerebellar tumour has recently been described.

VIII.   Cases of Graves' disease...in which one eye only is affected with proptosis.

IX.   Apparent exophthalmos.

These conditions may now be described in detail.

I.—SIMPLE HYPERTROPHY.

(1.) *Fat hypertrophy.*—Without any definite tumour formation, hypertrophy of the orbital fat does rarely take place, and it requires but little addition to the already existing contents of the orbit to produce exophthalmos. Hutchinson[10] describes a case in which this condition was so marked that the lids could only insufficiently protect the cornea, ulceration and loss of the eyeball resulting. The other orbit, becoming similarly affected, was treated with ice applications externally, combined with the administration of iodide of potassium internally.   Under this treatment the condition quickly improved, and the eye returned to its normal position in the orbit.   A feature which complicates this case is the fact that the lachrymal gland was enlarged, as also the parotid gland and lymphatic glands of the neck, but Hutchinson insists that the causal condition of the proptosis was hypertrophy of fat.

The treatment of this condition where the diagnosis is certain must be directed towards reducing fat formation by means of the administration of an alkaline hydrate (*e.g.* KHO) in solution, or, as in the above case, with potassium iodide and local cold applications.   Some help may be given by removal of some of the fat, the site of operation being dependent upon the direction of displacement of the globe.

(2.) *Hypertrophy of bone.*—This may be present as a general condition affecting all the bones of the face, or only local.   There is not a great deal of distinction between the cases described as hypertrophy of bone, or hyperostoses, and exostoses, but in the former there is not a definite tumour formation.   Virchow attributed them to a traumatic or syphilitic origin.   Gunn[11] records a case in which there was symmetrical bony enlargement of the upper half of the face causing double exophthalmos and complete anosmia.   Mackinlay[12] described an interesting unilateral

hypertrophy of the face involving the left frontal, malar, and superior maxillary bones coming on in a lad of 10 years of age. Silcock[13] operated on a case of this nature, which was at first diagnosed as sarcoma of the frontal bone. At the operation it was found that the frontal sinus was entirely obliterated, its place being taken by soft porous bone. The orbital plate of the frontal bone was fully half an inch thick, and it was impossible to remove the whole of the hypertrophied bone. Considerable improvement in the facial appearance and general condition of the patient followed removal of as much bone as was considered advisable.

Treatment : If the case is one of extensive bilateral affection, no treatment is of any avail. In the more localised cases removal of the whole or part of the hypertrophied bone may cause considerable relief to the exophthalmos and any consequent diplopia, in addition to improvement of the facial aspect.

(3.) *Hypertrophy of the lachrymal gland* is a condition occasionally found, three cases in this series being due to that cause. The proptosis is then associated with some inward displacement as well. In the early stages the hypertrophy may affect only the deep part of the gland, and no swelling may be detected ; later on, a swelling is felt, and seen, in the upper and outer angle of the orbit, behind which it is impossible to get the finger. The differential diagnosis from innocent tumours of the gland may be impossible to make without operation, but malignant disease may usually be excluded by the much slower progress of the case and the lack of any surrounding infiltration. Mention may be made of the great difficulty in being certain whether the swelling is solid or cystic, since the gland retreats very easily before the palpating finger, and also sometimes, as in a case of Mr. G. B. James, under the author's observation, some orbital fat —encapsuled or not—may lie over the tumour and produce a typical sensation of fluctuation. In these cases only operation will reveal the exact nature of the swelling.

Treatment consists in removal of the greater part of the hypertrophied gland as described in tumours of the gland.

II.—INFLAMMATORY.

Orbital cellulitis with abscess formation is one of the most frequent causes of exophthalmos, as revealed by examination of consecutive cases in hospitals, though, not being publicly recorded, they do not bulk largely in statistics. From the point of view of the origin of the inflammation, these cases are exceedingly interesting, though in many cases it is never exactly determined, seeing that if the patient recovers only an incomplete examination of the parts can be made.

The symptoms are, briefly, orbital pain which may become very severe, proptosis with much œdema of the lids and conjunctiva, and—if the abscess points forwards—a fluctuating swelling appearing at some part of the peri-ocular tissues. The inflammation may extend to the eyeball and kerato-iritis be caused, with subsequent deterioration of sight, or even loss of the eye. If the inflammation also spreads back, septic sinus-thrombosis and meningitis rapidly produce a comatose condition ending in death. Some cases throughout their course are plastic, and no pus can be detected even on repeated incision. Lawson[14] records four cases of this, three of which ended fatally from intracranial extension.

Cellulitis and abscess of the orbit may be divided into the following groups:—

A. Cases which commence in the cellular tissue of the orbit, their origin being ascribed to one or other of the following causes:—1. Traumatism. 2. Pyæmia. 8. Septicæmia. 4. Suppurating cysts.

B. Cases originating in the bony wall of the orbit or its periosteal covering.

C. Cases due to extension from the accessory sinuses of the nose, or from the teeth.

1. *Traumatism.*—Any penetrating orbital injury may set up a cellulitis here as elsewhere. This condition must, however, be a rare one, as no case occurs in this series. In an interesting case, recorded by Ross,[15] of puncture through the anterior nares, antrum, orbit, and thence to the middle fossa of the skull, an orbital abscess would probably have been produced, if there had

not been a free communication with the maxillary antrum which contained much pus.

2. *Pyæmia.*—Lawson[16] describes a patient who was suffering from pyæmia, with pain in all her large joints, in whom orbital cellulitis supervened on both sides. In this case death seemed to be due rather to heart failure than to intra-cranial extension. Hulke[17] refers to a case which occurred in a patient suffering from pyæmia after removal of the breast. At the autopsy there were distinct ante-mortem thrombi in the cavernous sinus and ophthalmic vein, and also in the veins of the choroid, with hæmorrhage. Lawson[18] also described a case occurring in a patient suffering from tonsillitis. Pain was the first symptom, soon followed by œdema and dusky redness of the lids, proptosis, and unconsciousness, with a temperature of 104°. No pus was found on making a free incision, and the patient died the next day. No autopsy was allowed.

Bronner[19] describes a case which may probably be classed under this form. A youth of twenty-one years had sudden onset of orbital pain followed by well-marked proptosis. On incision below the eyeball one drachm of pus was evacuated, but before this panophthalmitis had supervened, and the eye had to be removed. It was then found that the site of the abscess was Tenon's capsule, and the probable origin was suppurative otitis media of the other side. "Most cases," he remarks, "of abscess of Tenon's capsule are due to panophthalmitis. This case, however, is evidently one of primary abscess of Tenon's capsule which burst into the eyeball and caused panophthalmitis."

3. *Septicæmia.*—Hulke[20] mentions three cases which came on as a sequel of influenza, and one after measles.

4. *Suppurating cysts.*—Rockliffe[21] describes a case of hydatid of the orbit which, after causing proptosis for seven years, finally suppurated. The eye was removed and the cyst and contents evacuated.

The above cases of septicæmic and pyæmic infection of the cellular tissue of the orbit are of great interest, as they are so unexpected in their onset, and so frequently fatal in their consequences. Infection takes place by means of the blood

stream, and hence is very difficult, if not impossible, to prevent. Further, its rapid extension to the venous channels, and through them to the blood sinuses of the cranium, is almost impossible to check.

Treatment of orbital abscess is that of an acute abscess anywhere, viz., incision at the earliest possible moment. The importance of the venous and lymphatic relations makes it most imperative that the process should not be allowed to extend. As soon as the presence of pus is reasonably suspected an incision should be made in the conjunctiva, and a knife passed deeply into the orbit. The situation of the incision will depend upon any indication of the presence of a tumour. If none can be felt on deep palpation, and the displacement is simply a forward one, it will be preferable to make the incision on the outer side of the eyeball, and if there is much proptosis great assistance may be gained by cutting the outer canthus (canthotomy), and so allowing a free digital examination of the orbit. Moreover, an incision here will avoid venous channels more than it would if it were made on the inner side. If no pus be yet reached, it may be desirable to get within the muscular cone and examine around the optic nerve. For this purpose tenotomy of the external rectus muscle must be performed, sutures being passed in on either side of the line of incision prior to the section being made, so that the continuity of the muscle may be secured later on. If pus be found, drainage must be provided for until there is no further discharge.

B. The next class of cases of acute orbital abscess is one in which the origin is a primary inflammation of the orbital bony wall or its periosteal covering. Whether this is at all of frequent occurrence is difficult to say, as in many recorded cases no systematic examination of the teeth and the accessory sinuses of the nose has apparently taken place. In two cases which some years ago came under the author's observation, bare bone was felt by a probe inserted, but no further investigation of the nose was made. In these acute cases simple incision and drainage often effects complete cure.

Chronic orbital abscess also arises from disease of the periosteum and bone when these structures become the seat of tuberculous and syphilitic affections. In the early stages of these manifestations, a solid or semisolid tumour is present, and upon appropriate treatment the progress may be arrested and cure completed without the tumour breaking down. An exceedingly interesting case of this description came under the author's care at the Royal Eye Hospital, and was transferred to Guy's Hospital for treatment.

The following notes are from a paper read at the Ophthalmological Society by Mr. Ormond.[23] The patient was a healthy lad æt. 7 years. The history given was that on July 18th, 1907, his mother noticed that the lids of the right eye were swollen as if the boy had been stung by a mosquito. She treated the condition with various homely remedies with no beneficial results. The boy's medical history and the family history have nothing in them that throw any light upon the present condition. When first seen at the hospital the right and left upper eyelids were in a condition of ptosis, the right much more so than the left, and there was proptosis of both eyes, much more marked on the right side than the left. The right eye was turned downwards and outwards, and movements upwards and inwards were limited. There was a distinct mass to be felt in the right orbit just under the bony margin at the upper and inner angle, displacing the eyeball. The mass felt firm and elastic, the skin moved freely over it, and was a little browner in colour than the skin of the left eyelid. The conjunctiva of the upper fornix was swollen and hyperæmic. There was no optic neuritis, but the retinal veins were full and engorged. Vision was $\frac{6}{9}$. The ptosis and proptosis of the left eye were slight but distinct, and vision $\frac{6}{6}$. Under the supra-orbital margin of the left orbit, close to the supra-orbital notch, a distinct tongue of hard elastic material could be felt, and this suggested that the mass in both eyes might be due to a periostitis.

A general anæsthetic was given, and a piece of the growth was removed from each orbit and examined microscopically It was found to consist of inflammatory material infiltrated

with small round cells, and amongst this mass were numerous giant-cells, as well as an area suggesting caseation. There was nothing in the nature of a growth, either malignant or simple, and a more hopeful view of the prognosis was at once taken.

The other half of the tissue from the left orbit was inoculated subcutaneously into a guinea-pig of 370 grms. weight by Dr. Eyre. The experimental guinea-pig died thirty-eight days later, its weight being 250 grms., showing a loss of 120 grms. body-weight during the course of infection. At the post-mortem examination the animal presented a typical picture of general tuberculosis. The site of inoculation was occupied by a large collection of caseous material in which tubercle bacilli could be detected microscopically. The inguinal, femoral, and lumbar glands were much enlarged. The liver was studded throughout its substance with small caseous nodules (tubercles), and the spleen, which was much hypertrophied, also contained tubercles. As a result of this inoculation experiment we are able to say conclusively that the orbital tumour contained tubercle bacilli, and from the consideration of its situation and course, and of the histological sections of the portions of the tumour removed, we are inclined to regard the lesion as, primarily, a tuberculous periostitis.

The patient was treated with tuberculin injections at intervals for six months. When seen recently (May, 1908) there was neither proptosis, ptosis, nor loss of movement in either eye.

Cross[23] records another case further advanced in which, on opening the orbit by means of Kronlein's operation, a tumour the size of a hen's egg was found, "partially encapsuled, but closely attached to the eyeball and involving the orbit to such an extent that it was decided to eviscerate the contents." This was subsequently done, and the patient did well with the exception that a small exfoliation of bone occurred at one spot.

Other tubercular cases break down more rapidly and produce troublesome sinuses, which may persist for many months, eventually healing after exfoliation of bone and leaving a drawn-up scar over the site of the sinus. One at present under

Mr. James' care at the Eye Hossital has been in this condition for many months, in spite of scraping, tuberculin treatment, and sequestrotomy.

Rockliffe[24] described a case under his care of a man, æt. 64, in which an extreme degree of syphilitic periostitis was present. The eyeball was protruded three-quarters of an inch, but vision remained good, and improvement rapidly took place upon administration of potassium iodide in doses of gr. xxx., but the condition had not disappeared when the patient died of acute bronchitis. No autopsy was allowed.

Another case of gummatous periostitis of the orbit was in Guy's Hospital. The proptosis was very marked, and an attempt was made to remove the swelling, but ulceration of the cornea had already commenced and the eyeball was lost.

The treatment of cases of acute necrosis of bone in the orbit is the same as that of acute pyæmic abscess. Subsequently sequestrotomy may be necessary. Tubercular tumours which have not broken down will best be treated by the "open-air" method, combined with tuberculin injections based upon the estimation of the opsonic index. If caseation and breaking down occur, the abscess must be opened, the bone scraped if possible, and the case treated on similar hygienic lines.

If the case be one of syphilitic periostitis, every effort must be made to induce absorption of the gummatous material by the administration of potassium iodide, combined, if necessary, with mercury in some form.

C. Abscesses of the orbit caused by extension of inflammation from (1) the accessory sinuses of the nose, or (2) the upper jaw around inflamed teeth sockets. Much attention has been drawn to the nature of these cases of late. Birch-Hirschfeld[25] states that of 648 cases of orbital inflammation nearly 60 per cent. were secondary to suppuration in one or more of the nasal sinuses. Of the latter, the frontal sinus was most affected (29·8 per cent.), then followed the maxillary (21·8 per cent.), ethmoidal (20·5 per cent.), and sphenoidal (6·1 per cent.). In 14·7 per cent. several cavities were involved simultaneously. The process may spread from the nasal sinus to the orbit by way of connecting

veins, or a circumscribed abscess may form, which is at first
subperiosteal, but later bursts through into the cellular tissue.
So long as the abscess remains subperiosteal, the cellular tissue
of the orbit may escape.

If it is the posterior ethmoidal cells, or the sphenoidal sinus
which are involved, probably the first and a constant symptom
is a relative central scotoma for colours; in other words, a
retro-bulbar inflammation of the optic nerve. Later, there may
be a marked neuro-retinitis from the inflammation spreading along
the nerve to the retina. This may entirely subside on appropriate
treatment, as in a case of Knapp's,[26] in which, before operation,
vision = $\frac{20}{70}$, and afterwards vision was normal.

It is impossible here to give details of the pathology of diseases
of the accessory nasal sinuses. Suffice it to say that these air
spaces are found to be affected very frequently, *e.g.* in pneumonia,
syphilis—congenital and acquired—catarrhal affections of the
nose, influenza, and specific fevers. Fish[27] states that sinus
empyema is found in nearly all fatal cases of influenza and
measles. In some cases, dilatation of a sinus, owing to blocking
of its aperture, takes place without the inclusion of septic
organisms. In this case a mucocele is produced, consisting of a
slowly increasing bony swelling, its locality depending upon the
sinus affected. Several of these have come under the author's
observation and care. In one case of Mr. Eason's at Guy's
Hospital the patient was a woman who had a slowly growing tumour
at the upper and inner angle of the orbit. At first it was quite
hard, but at the time of observation it had become soft. The eye
was displaced down and out. Complete cure followed the
opening of the frontal sinus by Mr. Steward from the nose, and
draining it. Another patient, a gentleman, came under the
author's care for a small hard tumour in the same situation.
Any operative exploration was declined, so potassium iodide was
administered. After three months' treatment the tumour became
soft and fluctuating, and was obviously a mucocele either
of the frontal or ethmoidal sinus, but the patient still declined
operative treatment.

These mucoceles may terminate in one of three ways:—

1. By bursting into the nose produce spontaneous cure;

2. By pointing along the wall of the orbit and finally discharging externally with a cure;

3. By becoming infected with pyogenic organisms causing empyema, which in turn may burst into the nose or orbit. This latter, in addition to acute sinusitis, is a frequent cause of orbital abscess, only it is usually of a more chronic nature than in the other class, and it is not accompanied with the same amount of œdema.

Recurrent attacks of orbital abscess without much œdema point to a condition of empyema of a sinus discharging its contents into the orbit. Two cases of this kind have come under the author's notice, in both of which ethmoidal sinusitis was finally found. One case was cured when the sinuses were cleared out, and the other is still under treatment.

Another point which may be noticed is, that this sinus infection is not limited to adult life. Evans[28] records the case of an infant eight weeks old in which, on incising an orbital abscess below the eye, an opening was found into the region of the maxillary sinus and thence into the nose. Quick recovery followed the treatment. He also records a case of a girl of two years with ethmoidal disease after measles, causing cellulitis and destruction of the eyeball. Van den Wildenberg[29] records the case of a swelling which occurred at the internal and inferior border of the orbit three days after birth. This was soon followed by marked exophthalmos, the formation of three fistulæ and purulent discharge from the nose. By curetting the ethmoidal cells and maxillary sinus cure was obtained. He considers the conditions due to congenital syphilitic necrosis of the maxilla and ethmoid.

Treatment consists in dealing with the nasal condition, and many cases have been recorded in which all the symptoms of acute orbital abscess have cleared up on adequate treatment of the nose.

The maxillary sinus may be drained through the socket of a tooth. Better still, an opening may be made into its antero-external wall with a burr, and the cavity curetted freely.

The ethmoidal cells are more difficult to reach. The following routes of access may be used :—

(1.) Orbital (Knapp).

(2.) Endo-nasal (Grumvald).

(3.) Trans-maxillary (Laurent).

(4.) Facial-resection of nasal bones (Moure, Joubert).

The sphenoidal sinus is rarely affected alone, and hence the ethmoidal cells are first cleared, so that the routes of access are :—

(1.) Orbito-ethmoidal.

(2.) Facio-ethmoidal.

(3.) Transverse-maxillary.

The frontal sinus may be opened from outside or through the nose. The following brief résumé of operative measures is from Lack's book on disease of the nose.[30]

Schaffer advocates puncture of the sinus from below through the nose. This may be done either from the middle meatus, or from above the middle turbinate. Considerable risk attaches to this operation owing to the impossibility of previously knowing the exact anatomy of the sinus, and two fatal cases have been recorded, one with perforation of the cranial cavity. One case has already been referred to as being treated in this manner with a completely successful result. Recently the operation has been done in a darkened room under the guidance of X-rays and a fluorescent screen. Still it is doubtful, considering the risks, whether the operation is justifiable. If the puncture is successful the sinus is drained and irrigated until all symptoms cease.

External operation. The main objections to this are that the operation is dangerous, cure of the discharge is uncertain, and the deformity may be great. If eye symptoms are present, however, some operation is a necessity. The following are briefly some of the more important methods.

Ogston's. A vertical median incision, trephining the anterior wall, enlarging the ostium, placing a tube from sinus into nose and sewing up incision.

Jansen's. Incision parallel to and a little below the supra-orbital margin, turning back the periosteum from the orbital roof

and removing the entire floor of frontal sinus. Drainage through the nose and externally.

Kuhnt removes the anterior wall, and after removing all the mucous membrane drains through nose and externally.

Killian removes the greater part of the anterior wall, but leaves the supra-orbital margin: the inferior wall is then exposed and removed. By this means a narrow bridge of bone is left in position which prevents the subsequent sinking in. He also chisels into the nose and, displacing the nasal process of superior maxilla, removes all the bone in front of a probe passed down through the ostium, replaces the bony flap, closes the lower part of the wound, and packs the sinus with iodoform gauze.

III.—Vascular Conditions.

1.—*Hæmorrhage into the orbit.* This condition as a result of injury is described in eleven cases in this series, most frequently in bullet or shot wounds of the orbit. Two of the cases were bilateral, the bullet traversing each orbit and severing the optic nerves, whilst one eyeball was ruptured posteriorly. Other agents causing the hæmorrhage were knives, forks, pipe stems, umbrella ends, etc.

The treatment of these cases resolves itself into the antiseptic treatment of wounds in general, and each injury will probably require a different method. Incision into the orbit, removal of injured tissue, and, if necessary, trephining the cranial cavity to let out pus, or effused blood, may be included under this head.

Another variety of case is spontaneous hæmorrhage into the orbital fossa. A child under Mr. Ormond at Guy's Hospital had sudden proptosis of the right eye, without any inflammatory symptoms or pain, and with no diminution of vision. A few days later epistaxis came on from the right nostril and the proptosis was afterwards noticed to be less, and within fourteen days had entirely ceased, the eye being to all appearance absolutely normal. The only treatment required in these cases is rest, protection of the eye, and the application of cold compresses.

Orbital hæmorrhage, spontaneous in origin, also occurs in infants who are the subjects of infantile scurvy—so-called scurvy

rickets. The disease usually attacks children between the ages of six and eighteen months, in the cold part of the year, and the main cause is deficiency of fresh food. The patients are wasted and ill, with, in some cases, the usual bony lesions of rickets. In all, hæmorrhages in various parts of the body are present chiefly beneath the periosteum. It is one of these sub-periosteal swellings which causes the exophthalmos. Spicer[31] describes three cases occurring at seven, eight, and nine months respectively, in two of which proptosis was marked.

The treatment of this condition is that of the scurvy which causes it. A healthy diet suitable to the age of the patient with some fresh orange juice and vegetables, and, in addition, carefully selected meat juice. Cod-liver oil may be required if the patient is much wasted.

2. *Intermittent vascular dilation.*—Under Mr. Doyne's care at the Eye Hospital, was a patient, æt. 73, in whom proptosis occurred whenever he stooped. Upon resuming the erect posture the eyeball resumed its normal position. Lang[32] records a case at the age of twenty which he saw, but which had existed since childhood, and was attended with considerable pain. There was consecutive atrophy of the optic nerve. The proptosis was also produced by pressure on the left jugular vein. There was no history of injury, and no bruit. He also mentions other cases from the literature, and one more was described by Priestly Smith[33] in the discussion which followed. Opinion varied as to whether these were due to the presence of a definite cavernous angioma of the orbit, or simply to a varicose condition of the retro-ocular veins. The fact that some of these patients, when in the erect posture, present a condition of enophthalmos of the affected eye, points to the absence of any definite tumour. The cause of this dilatation may be traumatism, or, in the absence of this, must be considered due to a congenital tendency. That the condition is not one of thrombosis is shown by the absence of any inflammatory symptoms, and the complete immediate return of the eyeball on the patient resuming the erect posture. In most cases the eyeball is not affected, and no treatment is required.

3. *Thrombosis of the intra- or retro-orbital venous channels.*— Coupland[24] classifies the causes as follows :—

(1.) Primary or spontaneous, including marasmic thrombosis ; (2.) Traumatic ; (3.) Inflammatory.

(1.) Marasmic thrombosis, he says, occurs at the extremes of life, especially in patients whose vitality is lowered by debilitating and exhausting diseases. He mentions cases in cancer of the uterus, phthisis, and severe infantile diarrhœa. The other primary cases occur " idiopathically " in people who otherwise seem perfectly healthy, and must be attributed to a special tendency of the blood to clot.

(2.) " Of traumatic causes of cavernous sinus thrombosis, fractures of the skull, with or without meningitis, are most common." He mentions three cases.

(3.) " The third group is the most extensive, for it embraces all those cases in which thrombosis of the cavernous sinus is clearly secondary to lesions in parts more or less directly connected with the sinus." Recent research has revealed the fact that many of these cases start as inflammation of the ethmoidal or sphenoidal sinuses. On the other hand, such various causes are mentioned as the following :—Extension from the ear by way of the lateral sinus, from the facial veins, pterygoid veins, phlebitis originating in connection with the buccal, nasal, or pharyngeal cavities, and also primary or metastatic infections of the orbit, the thrombosis spreading back from the orbital veins. Cases presenting each of these origins were contained in this series.

The symptoms Coupland classifies into two groups :—(1) those which depend upon obstructed circulation, and (2) those due to nerve interference. Unilateral at first, the symptoms often become bilateral subsequently.

(1.) Symptoms due to obstructed circulation. Proptosis is a most constant symptom, but very variable in its degree. Occurring at first from venous obstruction behind the orbit, its onset may be sudden, and as the collateral circulation through the facial and pterygoid veins increases, the proptosis may decrease in amount. Later, when the obstruction involves the orbital veins, the proptosis becomes more marked and persistent.

Œdema is usually marked in the inflammatory cases, but less if at all in the traumatic or marasmic cases. Pain may be an early and severe symptom. It is usually deep-seated behind the eyes, but soon there is in addition severe headache, whether from some increased intracranial tension or not is difficult to say. Sometimes for a little while there is no other sign present than this pain. Venous hyperæmia and choked disc occasionally occur, but it is a remarkable fact that in these cases there is not, as a rule, any dilatation of the retinal veins, and the vision in the eye continues good as long as the patient remains in a fit state to be examined. This absence of dilatation can only be explained on the ground of the free communication which normally exists between the ophthalmic veins and the angular, frontal, and pterygoid veins. The optic nerve is often found bathed in pus, and doubtless, if careful examination could be made, the symptoms of a retro-bulbar neuritis could be found, but the patient is too ill for the attempt to be made. Papillitis is usually not marked, if present at all. As a rule the case terminates before the thrombosis has time to spread to the cervical portion of the internal jugular vein ; one of the patients died suddenly. Meningitis and cerebral abscess may occur, and the former is generally present in the cases which are fatal. It produces its usual symptoms.

(2.) Symptoms produced by pressure on the nerves as they pass through the walls or within the cavity of the sinus are often present. The first division of the fifth nerve is early affected, as shown by frontal and supra-orbital pain. A less marked symptom due to this nerve being affected may also be present in haziness of the cornea, which may become insensitive. The third, fourth and sixth nerves may be affected together or singly. With third nerve involvement only, there are ptosis, external strabismus, and dilatation of the pupil. When the fourth and sixth also become involved, complete ophthalmoplegia—internal and external—is a prominent sign.

Snell[35] records a case of a medical man in whom the origin was a pustule on the upper lip. Cellulitis spread from this to the infra-orbital tissues, and then into the orbit, leading to

thrombosis of the intra-orbital veins with extreme œdema and proptosis, and extending to the cavernous sinus, circular sinus and, finally, cavernous sinus of the opposite side, with subsequent proptosis of that eye, showing involvement of the veins of the other orbit from behind. Death took place from coma, but no autopsy was allowed.

Ethmoiditis. A case came under Mr. Ormond's care recently at Guy's Hospital, in a young man æt. 24. He came up to the out-patient department with a small swelling at the side of the nose in front of the inner canthus of the right eye. Two days later this was larger, and on being incised it yielded a few drops of pus. Through the incision a probe was passed back and came upon bare bone at the inner side of the orbit. The incision was enlarged and more pus evacuated, but within two days unconsciousness supervened, and the patient died. At the autopsy pus was found in the ethmoidal cells, cavernous sinus, and circular sinus. There was no meningitis. The jugular vein was not thrombosed.

Sphenoidal Sinusitis. Thompson[26] records a case in which, during life, he saw pus exuding from the sphenoidal sinus, and enlarged the ostium, scraping out the contents and packing the cavity. The septic process had, however, spread to the blood sinuses, and death supervened. At the autopsy the cavernous sinuses, the petrosal sinuses, and the lateral sinuses were filled with almost undiluted yellow pus. The right sphenoidal sinus was the only one of the accessory sinuses diseased, and it was of a size admitting the tip of the little finger.

Tonsillitis. Jessop[27] records a case of thrombosis of the circular and cavernous sinuses arising in a case of quinsy. At the autopsy the accessory nasal sinuses were all perfectly healthy.

Treatment. The treatment of thrombosis of the intra- and retro-orbital venous channels is extremely unsatisfactory. In the marasmic group the thrombosis is almost only a symptom, and attention must be paid to the general condition. Probably only in those suffering with excessive diarrhœa will treatment avail. Here an attempt must be made to check the intestinal

process, and to increase the quantity of water in the system by means of injections, either per rectum or subcutaneously. Those cases of thrombosis which are septic in origin are probably hopeless from the commencement. Hence the great treatment here must be prophylactic, every case of inflammation of cellular tissue in the region of the eye being carefully treated on antiseptic lines, to facilitate the exit of pus at the earliest possible moment. Also any case showing symptoms of inflammatory lesion in or near the orbit should have a thorough examination made of the accessory nasal sinuses, with a view to radical treatment in the case of one or the other of these being the seat of disease. Some idiopathic cases which present symptoms of an aseptic thrombosis of these sinuses recover. Coupland,[3x] in his paper already referred to, describes a case of his own, in which, after symptoms of thrombosis in the cavernous sinus had existed for some time, the patient got much better and left hospital. Subsequently the symptoms recurred and meningitis set in, leading to a fatal issue. At the autopsy an old shrunken clot was found in the cavernous sinus of the left side, and a recent purulent softened one in that of the other side. The circular sinuses were full of pus and caseous material. There was recent basic meningitis.

4. *Pulsating exophthalmos.*—This is one of the most interesting affections of all those causing proptosis, owing to the variety of pathological conditions which cause it. The following complex of symptoms is present. The eyeball is protruded to a very varying degree. Upon palpation with the fingers, a tumour may, or may not, be felt in the orbit, but distinct pulsation of the eyeball itself, and of the surrounding parts, is felt; and upon the application of a stethoscope to the eyeball or tumour, and in some cases to the temporal region, blowing murmurs and a continuous whirring and rumbling sound are heard. These sounds are also markedly audible to the patient, and cause him more annoyance than the proptosis. Frequently upon pressure being exerted upon the eyeball, it can be pressed back into the orbit, a point in which this affection differs from all others causing proptosis, with the exception of some vascular tumours.

Furthermore, pressure upon the common carotid of the same side obliterates or greatly diminishes the pulsation and its accompanying noises. The effect upon the eyesight is variable, and depends probably upon the amount of pressure produced upon the optic nerves, and the amount of dilatation of the retinal vessels.   This latter condition is seen in ophthalmoscopic examination of the fundus, in addition to the optic neuritis which may be present.   Later on, these conditions may lead to atrophy of the disc and great deterioration of sight, even though the primary condition has been cured.   Paralysis of the ocular nerves is but rarely reported.

As to the pathological lesion causing the condition, Jack[39] states that in only thirty-three cases in all has an autopsy been performed.   Of these he gives the following incomplete list :—

Rupture of internal carotid artery into cavernous sinus	7
Tumours	5
Aneurism of internal carotid artery	3
Aneurism of ophthalmic artery in orbit...	2
,, ,, ,, behind orbit	1
Thinning of internal carotid artery	1
Internal hydrocephalus	1
Orbital encephalocele	1
" No aneurism or arterial lesion "	6
	27

It will thus be seen that of the cases with vascular lesion by far the greater number are due to disease behind, and not within, the orbital cavity.

The first case on record, and one which was cured by ligature of the common carotid artery, was read by Travers,[40] in 1809, at the Medical and Chirurgical Society.   Since then a total of 260 cases has been recorded.   During the last ten years only two cases of this affection have been in the eye wards at Guy's Hospital.   During a similar period one case was in the wards of the South London Eye Hospital, whence it was transferred to the London Temperance Hospital for ligature of the common carotid artery.   Possibly other cases were seen in the out-patient

department, and likewise transferred to general hospitals for general surgical treatment. Many of the patients afflicted with this condition definitely date the onset to some injury to the head. Rivington,[41] in an analysis of 73 cases, found that 41 were traumatic in origin, and 32 idiopathic. Falls were the cause in 19 cases, and punctured wounds in 5, whilst of the 41 traumatic cases, 33 had either certainly or probably suffered from fracture of the base of the skull. The idiopathic cases which are due to some primary vascular disease generally start later in life than do the traumatic ones. Occasionally the disease is bilateral, even in traumatic cases.

The onset of symptoms varies. In some cases it is gradual, in others quite sudden and accompanied with violent pain and a loud noise in the head, which is variously compared to a "sudden snap," the "report of a pistol," or "a blowing noise." In the traumatic cases the onset may be masked by the general symptoms of injury to the head, but an interval of a few weeks may elapse before they show themselves. An interval of years is very rare.

Differential diagnosis as to the exact lesion present is exceedingly difficult, and the following are hints taken from Rivington's paper:—

(*a*.) The sudden onset with pain and loud noise points to rupture of an aneurism, or to its sudden formation.

(*b*.) The presence of paralysis of the orbital nerves points to an aneurism, or to an aneurism which has burst, and its clotted blood pressing on the cavernous sinus with its contained nerves.

(*c*.) Complete loss of vision at the outset, and failure to recover it after ligature or digital compression, would favour the supposition of an aneurism of the ophthalmic artery, rather than of the carotid.

(*d*.) The continuity of the bruit points to an arterio-venous aneurism, and an interrupted one to true aneurism.

Treatment. The fact that some cases make no change for many years, and that about twenty-one cases of spontaneous recovery are recorded in the literature, should make one conservative in treatment for some time in those cases which

are not causing severe symptoms. The treatment, then, may be divided as follows :—

(*a.*) Medicinal. The patient is here treated in the same manner as one with an aneurism of the aorta, by rest in bed, low diet, and administration of potassium iodide gr. xv., t.d.s. In addition small doses of digitalis may be given, and ice applied locally.

(*b.*) Digital compression of the common carotid artery. This may be carried out in conjunction with the above medical treatment. Cant[42] records the case of a man, æt. 36, with pulsating exophthalmos after a kick on the eyebrow, treated by this means. In addition to the medical treatment, digital compression of the common carotid, half an hour at a time, for three and a half hours daily, was employed for nine weeks. At the end of that time the tumour was less and the noises had greatly diminished. Six months later he was quite well, his symptoms had disappeared, and only slight proptosis remained. In other cases the digital compression is employed at intervals, so as to allow of the vessels of the other side enlarging sufficiently to prevent cerebral anæmia when, later, the common carotid artery is tied.

(*c.*) Injection of gelatine into the subcutaneous tissues for the cure of aneurism was instituted by Lancereaux and Paulesco. Beauvois[43] recommends it as "safe, efficacious, and easy of application." Its action is by its introduction into the blood to render the blood more coagulable and favour the natural progress of cure by the deposit of blood-clots in aneurisms. The possibility of clotting elsewhere must be remembered, as several accidents of this kind have occurred. Great care must be taken to sterilise the solution, some cases of tetanus having arisen. A 2 to 2½ per cent. solution is used, and 5 to 100 c.c. injected into the subcutaneous cellular tissue of the buttock fairly quickly, the process lasting about a quarter of an hour. Originally, the gelatine was injected into the orbit, but this is a highly dangerous proceeding. The number of injections necessary averages twelve, and they should not be repeated more frequently than every six

or eight days. One case took six months, and another took three months.

(*d.*) Ligature of the ophthalmic artery within the orbit. Lewis⁴⁴ records a case of this. "After a long and difficult dissection, under profound anæsthesia, the ophthalmic artery, which was curved upon itself, and at its widest part had the diameter of a man's little finger, was ligated in several places, until at last the vessel was tied just within the orbital cavity. Result was excellent. When seen three years after, there was no sign of proptosis and vision $= \frac{20}{30}$."

(*e.*) Ligature of the ophthalmic vein. Szimanosky was the first to suggest this treatment in some cases where decided indications of a dilated vein can be felt in the orbit, and Lasarew first practised it in 1898. It is seldom done only by itself, but in combination with ligature of the common carotid artery, or after that operation has failed. Alarming symptoms have been noted, but no fatal case due to this treatment has been recorded. Four successful cases are quoted by Gifford.⁴⁵

(*f.*) Electrolysis. In some cases of definite tumour felt in the orbit this method of treatment may be adopted. The applications require repetition and the use of chloroform. Robertson⁴⁶ mentioned a case very successfully treated by this means, and another partially successful. Clarke⁴⁷ mentions partial success in his case, but that the treatment had been repeated a dozen times, and sometimes the child was ill for a fortnight after the electrolysis.

(*g.*) Ligature of the common carotid artery. This treatment has been carried out in many cases. Stomans,⁴⁸ in 1898, referring to 95 cases, gave the following results :—

Cured	...	...	...	51
Improved ...	...	...	17
Unimproved	...	...	17
Died	...	...	...	10

Recent statistics do not alter this table materially. The fact that 10 per cent. of the cases die, shows that the operation is not without its dangers, though whether they are all " propter hoc " and not largely " post hoc," is not stated. Another real danger

which is apt to occur is that of cerebral softening, or even complete hemiplegia. Several cases of these complications are recorded. Two cases of pulsating exophthalmos have recently been at Guy's Hospital under Mr. Eason. One was in the left orbit, and was treated by ligature of the left common carotid artery by Sir Alfred Fripp. Pulsation ceased entirely, and the eye gradually went back into its natural position. Almost directly after the operation the patient complained of severe pain in the head. This gradually subsided, and the patient was discharged cured, but a few months later committed suicide, and no autopsy was obtained. Details of the operation need not be given, but mention must be made of the necessity for maintaining absolute recumbency for some days. The other patient—a woman—attended at Out-patients with pulsating tumour above the right eye, extending deeply into the orbit.

5. *Cavernous angioma.*—This is a tumour made up of an open sponge-like framework of fibrous tissue containing irregular cavities filled with blood. It is a rare condition to meet with in the orbit, but Emrys-Jones,[49] in 1889, collected about a dozen cases. In some instances the eyeball can be pushed back into its normal position, or if a tumour is presenting, it can be emptied by pressure. They are of slow growth and painless.

Treatment of these tumours may be by (1) enucleation, (2) electrolysis, (3) enucleation of eyeball and tumour, or even complete exenteration of the orbital contents.

Whitehead[50] reports a patient with extreme proptosis from this cause, with ulceration of the cornea. By dividing the external canthus and external rectus, the tumour, which extended to the apex of the orbit, was shelled out from a distinct capsule, and the rectus then re-united. Later Vision = $\frac{6}{9}$. Spicer[51] records an unsuccessful result of electrolysis in the case of a healthy young woman of twenty-three. Later the eyeball was removed, and finally the orbital contents needed complete exenteration. In this case the history given was that the affected eye was always more prominent than the other. On deep palpation in the orbit a mass was detected "like a bag of worms" in feel. No pulsation was present.

6. *Lymphangioma.*—Only three cases of this condition are mentioned in this series, two of which caused proptosis, the third an upward displacement of the eyeball. The latter was Weisner's[52] case, and the tumour was easily removed by an incision below the eyeball. Forster's[63] case was much more extensive, and the globe and tumour had to be enucleated together. Silcock's[54] case was treated by puncture with the galvano-cautery, which seemed to cure it for a while, but at the time of the last note it was as large as ever. When punctured a large quantity of serous fluid escaped. The origin of these tumours is doubtful. Weisner thinks that they are probably developed from some embryonic tissue.

IV.—CYSTS OF THE ORBIT.

Cysts are not at all frequently found within the orbital cavity.

1. *Hæmorrhagic cysts.* In spite of the frequency with which hæmorrhage takes place into the orbit, the formation of a true hæmorrhagic cyst seems to be exceedingly rare. Blood is nearly always completely absorbed. A case recently under Mr. James at the Eye Hospital, in which this provisional diagnosis was made, proved ultimately to be one of solid moveable tumour of the lachrymal gland. Only one hæmorrhagic cyst is found within this series of cases, and will be referred to again under tumours of the optic nerve.

2. *Parasitic cysts* — hydatid and cysticercus. The former occurs more often in the orbit than one would imagine. Five cases, with a possible sixth, are found in this series, while reference is made to over fifty cases. A considerable proportion of the cases have been children, Lawford[56] giving the average age as twenty years. Usually they are situated in the cellular tissue, but Brailey[56] described a case in Guy's Hospital of a girl æt. 2 in which many cysts were found in various parts of the body, the orbital one being situated within the substance of the superior rectus muscle. Cross[57] records one situated upon the optic nerve. Occasionally after existing for a long time they suppurate, as noted in the cases of orbital abscess.

Cysticercus. This is the bladder stage of the tænia solium, the tape worm which inhabits the human intestine. According to Monthus [58] sixteen cases in all have been placed on record as occurring in the orbit. They are painless elastic swellings causing displacement of the eyeball.

3. *Dermoids.*—Although these tumours are quite common around the margin of the orbit, especially at the region of the external and internal angular processes of the frontal bone, yet recorded cases deep in the orbit are very rare. They may grow into the orbit through a groove or opening in the outer wall as in cases by Lediard and Doyne.[59] By their gradual growth they may entirely protrude the eye, and erode the orbital walls, as in a case recorded by Chevallereau and Béal,[60] in which, at the operation, the finger, when passed into the cyst, penetrated 8·5 cm. from the upper margin of the orbit, that is to say, it encroached considerably upon the cranial cavity, through an aperture caused by erosion.

4. *Implantation cysts.*—Though these cysts occasionally arise in the orbit, they usually do not cause proptosis, as the injury which causes them generally also affects the eye, which is consequently removed or shrinks. Critchett and Griffith [61] recorded one such, about the size of a horse chestnut, arising after a penetrating orbital wound. The cyst was lined with stratified epithelium, and contained no hairs or glandular structures.

5. *Dacryops.*—This is a very rare affection. It consists of a cystic tumour in the upper and outer part of the upper eyelid, a characteristic sign being its increase in size when the patient weeps. The wall is extremely thin. The formation has been explained in two ways; either by the uniform distension and dilatation of an excretory duct of the lachrymal gland, or secondly, by the distension and expansion of the interstices of the cellular tissue. Lawson [62] describes a cyst which he considers as belonging to this class which caused proptosis. It was of the size of a pigeon's egg, was removed entire, and its walls were very thin and translucent.

Treatment. These cystic tumours require complete removal. Sometimes they can be dissected out without puncture. In other cases their removal is greatly facilitated by puncture. Sometimes Kronlein's operation, as described in the next section, enables them to be removed from behind the eyeball without injury to the latter organ.

V.—Solid Tumours of the Orbit.

Solid tumours of the orbit may be divided according to their nature into *A*. Innocent, and *B*. Malignant, and according to their situation into :—

1. Those which arise in the bony walls.
2. Those originating in the lachrymal gland.
3. Those which arise in the orbital cellular tissue. This class contains the greater number of tumours of the orbit.
4. Tumours originating in the optic nerve and its sheaths.

Six cases have come under the author's care or observation, four being sarcoma, one an adenoma of the lachrymal gland, and one diagnosed as a tumour of the optic nerve, the diagnosis not being confirmed, as the patient—a child of twelve—left the hospital, the parents refusing operation.

The size and rapidity of the growth of an orbital tumour usually point to its nature. The great danger of malignant growths is their rapid extension to the cranium through the normal foramina, or by erosion of the walls themselves. On the other hand, cases which originate within the cranium may, by extension, fungate into the orbit.

Of innocent tumours, the following are recorded in this series, and will be briefly referred to :—

1. Osteoma, or exostosis.
2. Adenoma, or fibro-adenoma.
3. Myxoma.
4. Lipoma.
5. Neuroma.
6. Plexiform neuroma.

Osteoma.—Twelve cases of this are recorded in this series. Nearly all of these were of the "ivory" consistence. The usual

position for them to occur is the inner or upper and inner wall of the orbit, the frontal bone being the one especially involved. The next most frequent site is the ethmoid, but the growth is so slow and painless at first that often the tumour has attained such large dimensions before being seen by a surgeon that the exact origin is very difficult to determine. In several of the cases in this series the tumour seems to have replaced the frontal sinus. A few of them are sessile, but most have a pedicle, which is much smaller than the greatest diameter of the tumour, as in a case recorded by Ogilvy,[63] in which the pedicle measured 0·5 cm. across, and the widest part of the tumour 2·5 cm. Unfortunately these tumours are not always confined to the orbit, but may extend either into the nose or into the cranium, in the latter case causing symptoms of cerebral compression. Another characteristic is their nodosity. They seldom have a smooth surface, and sometimes the sulci separating the nodes are so deep as almost to divide the tumour into two parts. The symptoms may be briefly described as displacement of the eye causing diplopia. the presence of a hard tumour, alteration of the refraction of the eye by pressure, with diminished vision and gradually increasing pain.

The diagnosis of these tumours, when seen in an early stage, is not by any means easy, as small swellings of a bony hardness may be due to either periostitis, mucocele, or osteoma. When the tumour is of larger size the diagnosis is more simple. The use of X-rays in the diagnosis of position and extent is now most valuable. The situation of the pedicle is often impossible to determine until operation is performed. ·

Treatment. The only treatment for these tumours is to remove them wholly or in part. If the tumour extends into the cranial cavity its complete removal is probably impossible, but the orbital part may possibly be removed, and this will relieve the eye symptoms, and prevent loss of the eyeball. In other cases the tumour may already be of such size within the orbit that it is impossible to remove it, and the only treatment which can be adopted is to remove the eyeball so as to relieve pain.

In operating for the removal of these growths three methods may be employed, (1) the hammer and chisel, (2) the electric drill,

(3) a Gilgi saw. The hammer and chisel, or gouge, is the method most usually adopted. It must be remembered, however, that the ethmoid is very thin, and liable to fracture. An incision is usually made beneath the eyebrow so as to leave as little scar as possible. When the periosteum is reached a groove is made round the pedicle, and then by levering the tumour an attempt is made to dislodge it. If the tumour has no pedicle, but is sessile, the amount of force required to chisel it off will probably be so great that considerable risk is run of breaking the skull. In this case it will be safer to drill the tumour in many spots where it arises from the bone, and then connect these holes with a chisel, and so remove the tumour. Sometimes the tumour can be removed by taking away the entire outer wall of the frontal sinus ; or the whole thickness of the skull at some part may have to be removed and the dura mater laid bare. If in doing this the ethmoidal sinuses be not opened, thus preventing infection from the nose, the case will with care run an aseptic course.

Of innocent solid tumours this series contains, besides osteoma already mentioned, the following :—Myxoma, lipoma, fibroma, adenoma, neuroma, plexiform neuroma, and lymphoma. As these tumours present the same characteristics in the orbit as elsewhere, only brief mention will be made of certain points. Pure *myxomata* are rare in the orbit. Juler [64] records a case in which the whole tumour was a mass of jelly. It had eroded the frontal bone, making an aperture into the cranium, but on histological grounds it was judged by a committee of the Ophthalmological Society to be a pure myxoma. *Lipomata* also are not common. Occasionally they may almost consist of a fibrous envelope containing an oily fluid, as in a specimen in the Royal College of Surgeons Museum. One case of *fibroma* following repeated attacks of œdema of the orbit is recorded by Batten.[65] Improvement followed removal of a small portion for examination, so that the origin of the tumour was not ascertained. *Adenomata* most frequently arises from the lachrymal gland, and indeed form a large proportion of all innocent tumours of that structure.

A so-called "*neuroma*" of the third nerve is described by Wherry.[66] The tumour had been two years or more growing, and had produced much proptosis. The eyeball was removed before the tumour, which, upon microscopical examination, was found to consist of fibrous tissue, as "neuromata" generally are. No statement is made as to following the nerve through the tumour. Plexiform neuroma is another tumour of nervous origin. It is also known by the names "cirsoid neuroma" and "elephantiasis neuromatodes." When seen in the orbit it is generally there by extension from the lids, in which it grows slowly and causes much disfigurement of the face. It is due to a plexiform enlargement of the nerve fibres and a fibromatous thickening of the endo-neurium. Four cases are contained in this series, *e.g.* Rockliffe and Parsons,[67] but the total number of cases recorded is small.

Malignant tumours found in the orbit may (1) take their origin from its tissues, or (2) invade it from surrounding structures, or (3) be produced by metastatic deposits. Each of these methods is illustrated by cases in this series.

Primary sarcoma of the orbit.—Twenty cases of this are contained in this series. The growth may commence in (1) the cellular tissue or muscles, (2) the periosteum or bone, (3) the optic nerve sheaths. Nearly all the varieties of sarcomata may be found, *e.g.* fibro-sarcoma, round-celled and spindle-celled, alveolar sarcoma, cylindroma, myxo-sarcoma, osteo-sarcoma, and lympho-sarcoma. Very few cases of the latter are on record as occurring in the lachrymal gland, but one case has recently been under Mr. Hosford at the Eye Hospital. The age of onset in sarcoma is frequently young, as is usual with sarcoma in general. One case under Mr. Ormond at Guy's Hospital was a boy of nine years of age. The only symptoms were proptosis and a feeling of fullness on the outer side of the orbit deeply situated. The nature of the swelling was only ascertained upon the performance of a Kronlein's operation. The wound there was then closed, and the contents of the orbit completely exenterated. Recurrence, however, took place in the temporal fossa, and the child died three months later. This early extension, or metastasis, is seen

especially in round-celled growths. Melanotic growths are usually extensions from the choroid or conjunctiva.

There are three groups of tumours somewhat resembling sarcomata, which it is somewhat difficult to classify satisfactorily. They are (1) *lymphomata,* (2) *chloromata,* (3) *endotheliomata.* Some group the lymphomata and chloromata together, and certainly they are very similar. Each is usually bilateral in the orbit, in addition to being found in various parts of the body ; in each blood changes are almost invariably present, and each is generally fatal from gradual failure, and not usually from extension to vital organs. On the other hand, the symptoms of chloroma are, according to Pfeiffer,[68] fairly well marked. He summarises them as follows :—(1.) Painful exophthalmos with consecutive optic atrophy. (2.) Affection of the ear with swelling of the temporal region. (3.) Acute lymphatic leukæmia with hæmorrhages into the skin and mucous membranes, and glandular swellings. (4.) The rapid course of the disease and the youth of the patients. Butler [69] describes a case of a girl, æt. 11, as follows :—Double proptosis, more marked on right side, bilateral optic papillitis : vision $= \frac{6}{8}$, each temporal fossa occupied by a semi-fluctuating swelling; liver, spleen, and lymphatic glands of normal size ; red corpuscles 3,000,000, white 26,000, the different count showing a lymphatic leukæmia, no hæmorrhages at first, but occurred later, especially from the right orbit ; death in two and a half months from onset. Post-mortem examination, chloroma inner surface of sternum, apex of each lung, whole length of spine, both ovaries ; right eye disorganised and small mass of chloroma deep in orbit ; lachrymal gland, temporal fossa, meninges, right cavernous and lateral sinuses, all the seat of chloroma of a green colour. Microscopically the growth was said to be a round-celled sarcoma, with an unusually well-marked stroma.

Endotheliomata are tumours which originate from the endothelial lining of lymphatic vessels or spaces. Distortion of the natural tissues rapidly occurs, and degenerative changes supervene, so that at some stages these tumours are classed with the sarcomata, and at others with the carcinomata. As a rule they

are only locally malignant, but Paton [70] describes a case which recurred after removal, and spread to the glands of the neck.

Malignant disease of the orbit occurring by invasion from surrounding parts is not infrequent. The growth may be sarcoma or carcinoma, and may commence in any of the adjacent structures, as maxillary sinus, frontal bone, lids, etc. Two cases of this have come under the author's care, one at Guy's Hospital, in a man æt. 54, who had suffered from symptoms of intracranial growth with subsequent double optic atrophy and double proptosis. An unsuccessful attempt was made to remove the tumour by Mr. Lane, the patient dying the following day. At the post-mortem examination an extensive carcinoma involving the floor of the anterior fossa of the skull, and invading the frontal lobes and orbits, was found. Another case was one of sarcoma of the floor of the anterior fossa, which spread into the left orbit and finally fungated out on to the cheek. The patient was a girl of seven.

Primary tumours of the optic nerve are divided into extra-dural and intra-dural. The condition is essentially one of early life, only four out of 102 cases of intra-dural tumours collected by Byers [71] occurring after the age of 25. The intra-dural are of more frequent occurrence than the extra-dural. In this series of cases the tumours were designated as myxoma, fibroma, hydatid cyst, psammoma, sarcoma, glio-sarcoma, endothelioma and glioma. Parsons [72] gives an account of eighteen recorded extra-dural ones, his own being an endothelioma.

The diagnosis between extra- and intra-dural tumours is usually impossible, and also unnecessary. The diagnosis of optic nerve tumours from other orbital growths is thus summed up by Byers [73] "As proptosis gives us the clue to the presence of an orbital growth, so an associated early and profound reduction of vision indicates, more than any other symptom, the presence of a tumour of the optic nerve. Taken together, these two symptoms, unilateral and early exophthalmos, with early amaurosis, are almost in themselves proof positive of the presence of the condition under discussion; but if in addition one has, as is

frequently the case, marked changes in the papilla, the diagnosis of a tumour of the optic nerve is practically certain."

Metastatic malignant tumours in the orbit are of very rare occurrence. Ridly[74] records a doubtful one of sarcoma. Axenfeld[75] recorded a case in which the deposit, secondary to mammary carcinoma, occurred in the muscles of the eye, causing progressive paresis. Later, proptosis supervened. By far the greater number of cases, however, of metastatic deposits occur within the eyeball itself, and Marshall[76] has collected 24 cases. The primary focus in the great majority was in the breast, but others arose from stomach, lung, and thyroid.

The prognosis in tumours of the orbit may be given in relation (1) to the eyeball, (2) to the life of the patient. Osteomata are very dangerous to the eyeball unless removed, as by their pressure they will interfere with its nutrition. They are less dangerous to life, though with intracranial extensions even this may be in danger. The other innocent tumours may each cause destruction of the eyeball or its sight, especially by such a degree of proptosis that the eyelids are unable to close over the eyeball. By this means ulceration of the cornea is induced, and this leads to deterioration of sight or even perforation of the eye. If these tumours are successfully removed without injury to muscles or nerves, the visual power of the eye may be quite unimpaired. Malignant tumours, on the other hand, unless early removed, will soon destroy both eyesight and life. Their removal must be very complete, and usually requires removal of the whole contents of the orbit.

Treatment of tumours of the orbit.—The treatment of osteoma has already been given. In the case of other tumours the following methods may be given :—

(1.) Incision is made over the site of the tumour where this is superficial. The finger is then inserted into the wound, and by means of blunt dissection with a metal instrument it may be possible to get behind the tumour and shell it completely out. This was the case in an endothelioma of the lachrymal gland, in the removal of which I assisted Mr. James. The incision was deepened mainly by tearing with dissection forceps until the

finger could be passed completely behind the tumour, which at length was pushed out of the wound just as a marble might be. Care must be taken to protect the eyeball and muscles as much as possible.

(2.) If a fullness be felt either at the inner or outer side without any definite tumour, but with sufficient grounds to suspect one, an incision may be made into the conjunctiva beneath the lids, and an exploration and blunt dissection similar to the last carried out.

(3.) In addition to this, the outer canthus may be split in order to give more room for examination and removal of growth. Also, in the case of tumours of the optic nerve, the external rectus may be divided. By this means Collins [77] removed a tumour of the optic nerve, together with a considerable portion of that nerve, without injuring or removing the eyeball, and without the necessity of performing Kronlein's operation. After this removal of a large part of the optic nerve, shrinkage of the globe has occurred in some cases, but in the majority its shape and tension are preserved, although hæmorrhages into it may occur immediately after the operation, and atrophy of the optic nerve necessarily follows.

(4.) Kronlein's operation. This operation, which is a temporary osteoplastic resection of the outer wall of the orbit so as to expose the depth of that cavity, was introduced in 1887. Since that date it has been performed many times by different operators for the removal of tumours, foreign bodies, and all substances in the posterior part of the orbit that offer a reasonable chance of being removed without sacrificing the eye, or injuring any part that is essential to the integrity of visual function. The following is a description of the operation. A curved incision is made from a point a little above and behind the external angular process of the frontal bone, downwards and forwards across that process to a point in front of the centre of the outer margin of the orbit and behind the outer canthus. From here the incision curves downwards and backwards across the outer margin of the orbit to a point about half an inch behind the temporal border of the malar bone and just above the zygoma.

The incision is carried down to bone along the outer orbital margin. The periosteum of the inner surface of the outer orbital wall is detached with a raspatory as far as the anterior end of the lower orbital fissure, into which a sharp-pointed probe is inserted to serve as a landmark. A wedge-shaped piece is now separated from the outer bony wall of the orbit by chiselling from the upper end of the margin obliquely down to the inferior orbital fissure, and then horizontally from the lower end of the margin of the outer bony wall to the anterior end of the inferior orbital fissure. The piece of bone thus circumscribed remains in contact by its edge and outer surface with the soft parts which are subservient to its nutrition. If the periosteum which lines the inner surface of the outer wall is not diseased, it has only to be split to expose the posterior part of the orbital cavity and any tumour contained therein. When the operation on the orbital contents is complete, the periosteum is united with catgut, the bone wedge replaced, and the skin united. Firm bandaging to keep the bone in place is necessary.

The dangers of the operation are (1) necrosis of bone, (2) fracture in chiselling, (3) sepsis. In addition, the scarring is a disadvantage, and often there is much paralysis of the external rectus. This latter is unavoidable. Cross[78] gives an account of five cases in which he performed this operation in one year, but two proved to be malignant, and another a broken-down tubercular mass, so that exenteration of the orbit was necessitated.

(5.) Removal of the eyeball and tumour together is often necessary owing to the close attachment. In this case the conjunctiva is cut all round, Tenon's capsule opened, the recti caught and severed, the optic nerve cut, and the tumour and eyeball then removed by cutting through the remaining connections.

(6.) Total exenteration of the orbit. This is required in malignant cases which start within the periosteal sheath, but are not removed early. An incision is made through the conjunctiva and soft parts down to the orbital margin in its whole extent, severing the periosteum completely. This latter is then peeled

from the orbital walls with a raspatory, and the orbital contents removed entire in one mass by cutting through all the structures at the apex and sphenoidal fissure. If the bone has become diseased, it should be scraped and rubbed with zinc chloride paste. Metastatic deposits require exenteration of the orbit to prevent much pain and foul discharge, though of course no hope of cure can be given.

VI. Traumatism.

Traumatism is not unfrequently a cause of exophthalmos of one eye. Rather, however, this condition should be called dislocation of the eyeball, as that organ lies outside the palpebral opening on the cheek. Wolff[79] describes a number of cases which occurred from the use of forceps in childbirth. Other cases occur in various ways, as in catching the eye on a gas bracket when descending a ladder, or from injury with a blunt tool, such as a screw-driver.

VII. Cerebellar Tumour.

Cerebellar tumour with proptosis. Parkinson and Hosford[80] describe a case of this, and state that only three other examples are recorded. It is uncertain as to the exact cause of the proptosis, some ascribing it to hydrocephalus and some to pressure upon the sympathetic plexuses.

VIII. Graves' Disease with Unilateral Exophthalmos.

This is a very uncommon condition, and one which needs care in diagnosis. Three cases have come under the author's care in which other symptoms of the disease were not marked, but in which the subsequent course of events proved the correctness of the diagnosis.

IX. Apparent Exophthalmos.

Lastly must be mentioned apparent exophthalmos. This is due to a variation in the size of the eyes. In a girl under the author's care, the left eye is hypermetropic, + 2 D., and the right eye is myopic − 25·0 D, giving a difference in the axial lengths of the eyeballs of probably 6 to 9mm. This causes a

marked apparent proptosis of the right eye, which may be masked by a concave glass.

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A NEW METHOD OF
ESTIMATING LACTIC ACID IN URINE.

By

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THE classical method of estimating lactic acid in physiological materials consists in weighing the zinc or other metallic salt obtained from the acid, after this has been separated by repeated extraction with ether. The objections to this method are that it is laborious, that ether extraction of lactic acid always involves some loss, especially with small quantities, and that the metallic salt obtained is liable to contain impurities, which are not recognised unless the percentage of the metal in the salt is determined. In 1908, E. Jerusalem[1] published a new method for estimating lactic acid, which, however, still involves a preliminary extraction with ether, and therefore does not present great advantages over the older method. Moreover, in this method, β oxybutyric acid forms a considerable source of error.

Hopkins, in his paper with Fletcher on lactic acid in amphibian muscle,[2] proposed a new test for lactic acid, which consists in heating with strong sulphuric acid, containing a trace of copper, and adding a trace of thiophene, when a purple colour is produced. This test is distinctive for α-hydroxy fatty acids, provided that pure sulphuric acid is used. In attempting to apply this test to urine I found its use rendered exceedingly difficult by the development

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[1] Biochemische Zeitschrift, 1908, xii., p. 361.
[2] Journal of Physiology, 1907, xxxv. p. 247.

of dark-coloured pigment on adding sulphuric acid, even after extraction with ether and decolourising with charcoal. As the reaction depends on the formation of acetaldehyde from the lactic acid, I tried distilling the lactic acid with sulphuric acid, and found that, on steam distillation with rather over 50 per cent. pure sulphuric acid, acetaldehyde is obtained in the distillate quantitatively. To the distillate so obtained any of the known tests for aldehyde may be applied, and the amount of aldehyde may be determined by a suitable method. At the suggestion of Dr. J. Wade, I tried comparing the colour obtained by the addition to the aldehyde of a measured quantity of Schiff's reagent (rosaniline hydrochloride bleached with sulphur dioxide) with that obtained with the reagent and known quantities of standard formaldehyde solution, and found the method very sensitive and sufficiently accurate.

The actual procedure is as follows :—

1st Stage.—The delivery tube of a 500 c.c. Jena distillation flask is so bent that it can be attached to a good vertical condenser, when the flask is sloped at an angle of 45°. 40 c.c. of the urine is placed in this flask, and 45 c.c. of nitrogen free sulphuric acid added rapidly from a dropping funnel, whilst the flask is shaken and cooled under the tap. The flask is then fitted with a rubber cork carrying a thermometer and an inlet tube for steam, so arranged that, when the flask is in position, both dip well into the liquid. The flask is then placed on wire gauze and attached to the condenser, whilst the inlet tube is attached to an ordinary steam generator. The receiver of the condenser is a flask of about 300 c.c. capacity, immersed in ice or cold water, and fitted to the condenser with a loose cork, or pushed right up against the base of the condenser jacket. A gentle stream of steam is then led into the flask, which is vigorously heated with a bunsen. When distillation has begun, which should be at a temperature rather below 140° C., the current of steam is reduced to a minimum and the flask rapidly heated to about 155° C. The current of steam is then increased, and the heat applied to the flask is adjusted to maintain this temperature with a variation of about 2° either way. When about 100 c.c. has collected, or when

the distillation has lasted nearly thirty minutes, the decomposition is complete.

2nd Stage.—The contents of the receiver are rendered just alkaline with 2 per cent. caustic soda, using litmus indicator, and made up with water to about 150 c.c. If on standing for a couple of minutes the liquid becomes acid again, it should be again made alkaline, and so on. The condenser is washed out, and a flask with a 100 c.c. mark in the neck is placed as receiver, with the same precautions as before. The neutralised distillate is redistilled till about 50 c.c. has collected. This second distillate is then stoppered and placed in a bath at about 15° C. for a short time.

3rd Stage.—A standard solution of formaldehyde is prepared as follows: 10 c.c. of commercial 40 per cent. formaldehyde is diluted to 100 c.c. This solution will keep practically indefinitely, and should be standardised by the iodine method of Romijn. For use this solution is diluted 100 times, when it should contain nearly ·4 mg. formaldehyde in 1 c.c., and will keep practically unaltered for a week. The Schiff's reagent is prepared by adding 100 c.c. of water to 1 gm. rosaniline hydrochloride (finely powdered) and passing in sulphur dioxide from a syphon, till the dye just dissolves to a yellow solution, when the liquid is very nearly saturated with sulphur dioxide.

The day previous to the determination a series of stoppered 100 c.c. flasks is prepared containing ·5 c.c. of the reagent and 2 c.c., 3 c.c., 4 c.c., 5 c.c. respectively of the dilute standard formaldehyde solution, made up to 100 c.c. with water. These are placed in a dark cupboard till required. The colour develops very slowly, but will keep unaltered for two days after the first twelve hours.

To the distillate from Stage 2 is added ·5 c.c. of the reagent, the volume is made up to 100 c.c. with water, and the contents of the flask well mixed.

The flask is then stoppered and placed in a glass vessel containing water at 15°C. and left in diffuse daylight for thirty minutes. With acetaldehyde the colour comes fairly rapidly, but proceeds to fade slowly as soon as the maximum is reached.

For the colorimetric determination the same depth of the aldehyde liquid is compared with the two formaldehyde liquids which are nearest to it in concentration of colour.

The calculation is best described by an example.

	Formaldehyde 3 c.c.	x	Formaldehyde 4 c.c.
Readings of equal depth of colour	2·42 cm.	2 cm.	1·46 cm.
10 ÷ readings	4·13	5	6·85

These figures represent the relative concentrations of colour of the solutions employed.

Then x is equivalent to 3 c.c. $+\dfrac{5 - 4\cdot13}{6\cdot85 - 4\cdot13} = 3\cdot32$ c.c. of formaldehyde solution per 100 c.c.

40 c.c. of the urine therefore contain lactic acid equivalent to $3\cdot32 \times a$ milligrammes of formaldehyde where a is the standard value of 1 c.c. of the dilute formaldehyde solution, and should be nearly ·4 mg.

If on mixing with the reagent the distillate gives a colour much greater than that in the 5 c.c. formaldehyde flask, it may be rapidly diluted to say 200 c.c. and a proportionate amount of the reagent added, or another distillation with less urine and water added to make up 40 c.c. must be undertaken.

In dealing with very small quantities of lactic acid, such as occur in normal or nearly normal urines, it is more convenient to make the distillate up to 50 c.c. with the addition of ·25 c.c. of the reagent, and calculate accordingly.

The reagent loses sulphur dioxide rather readily, so that it must be kept closely stoppered, and must be resaturated occasionally. The standard flask with ·5 c.c. of the reagent and 5 c.c. of the dilute formaldehyde should be of such a depth of colour, that by the colorimeter 1·5 cm. with a variation of ·2 cm. either way is equivalent to ·7 cm. $\dfrac{N}{100}$ potassium permanganate (the colour is not a close match). If the reading is less than this, more sulphur dioxide must be passed in, if greater, sulphur dioxide must be allowed to escape.

The method was standardised by using recrystallised calcium lactate, with the result that ·4 mg. formaldehyde = 3·435 mg.

lactic acid. Assuming this result, other observations gave the following :

Lactic acid used.				Found.
12·60 mg.	...	...	...	11·93 mg.
25·60 „	...	...	...	24·46 „
12·80 „	...	...	...	12·40 „
36·98 „	...	..	...	36·57 „

The accuracy of the conversion of lactic acid into acetaldehyde was tested by making solutions of "absolute aldehyde" and colorimetrically determining these against the formaldehyde solution. The result of two series of such determinations was that ·4 mg. formaldehyde was equivalent to 1·765 mg. acetaldehyde, which would theoretically correspond to 3·61 mg. lactic acid. The difference between this figure and that for lactic acid direct, 3·485 mg., is accounted for by manipulative loss in dealing with the absolute aldehyde solutions.

Lactic acid added to urine gave the following results :—
5 c.c. lactic acid solution determined directly 10·92 mg. lactic acid.
5 c.c. lactic acid solution added to 35 c.c. urine 12·27 „ „
85 c.c. of same urine alone ... ... 2·20 „ „
Lactic acid recovered from urine... ... 10·07 „ „

If the method be applied to about 80 c.c. of normal urine (sp. gr. 1020), a small, but measurable, result is obtained. This amount varies with the specific gravity of the urine, but is roughly the same whether the urine be passed by day or night. On the other hand, the output per hour is considerably greater during the day than at night.

Specific gravity of urine.			Lactic acid per 100 c.c.
1021 (night), J.H.R.	...	...	7·68, 6·27, 6·32 mg.
1020 „ E.L.K.	...	...	5·02
1019 (day), J.H.R.	...	...	5·68
1014·5 „ „	...	...	4·72
1013 „ „	...	...	3·97

J.H.R. Lactic acid in mg. per hour ... Day 4·34, 3·55.
„ „ ... Night 1·61, 1·89, 2·36.
E.L.K. „ „ ... Night 1·62.

Mild exercise, such as walking, produces practically no effect on the excretion of lactic acid, but when the exercise is violent the effect is very marked. For instance, the urine passed during one hour, at the beginning of which eight laps (33 laps to the mile) were run in 1 minute 40 seconds, contained 90·3 mg. lactic acid per 100 c.c., or 67 mg. lactic acid per hour. This extra lactic acid is all excreted in about half an hour from the cessation of the short period of exercise.

If the exercise be continued for a longer period, higher results are obtained, 600 mg. per 100 c.c. being the highest up to the present.

These results correspond very well with the conclusions drawn by Douglas and Haldane[3] from their observations on alveolar air during exercise.

Pathological urines.—Estimations were made on urines, kindly provided by Dr. French, from two cases of congenital heart disease with cyanosis, both of whom had previously been found by Dr. Pembrey and Dr. French to show low alveolar CO_2 and polycythæmia, to determine whether the deficiency of the supply of oxygen to their tissues was sufficient to cause a continuous excessive excretion of lactic acid.

As the patients were not in the hospital at the time, it was impossible to obtain the total urine. Both of them were up during the day doing light work.

		Specific gravity of urine.		Lactic acid per 100 c.c.
Case 1 (male)	…	1012 (day)	…	6·86 mg.
		1013 (night)	…	3·74 „
Case 2 (female)	…	1021 (day)	…	24·6 „
		1021 (night)	…	14·85 „

Case 1 is distinctly the more energetic of the two, and is probably the better compensated.

[3] Journal of Physiology, xxxviii., p. 420.

The following cases were all in the hospital and in bed
Except in the first case the amount of lactic acid is very little
different from the normal :—

Case of angina pectoris (male) admitted 4 days before with pulse 120 and cyanosis	Urine of 24 hrs. sp. gr. 1013	24·11 mg. lactic acid per 100 c.c. 19·7 „ per hour.
Two days later— patient quite comfortable	Urine of 12 hrs. (day), sp. gr. 1016	7·02 mg. lactic acid per 100 c.c. 3·51 „ per hour.
Case of pleuritic effusion (male), pulse 60–70, no distress	Urine of day, sp. gr. 1017 „ night „ 1017	6·13 mg. lactic acid per 100 c.c. 5·41 „ „
Case of failing heart (male), admitted day before. Pulse 70–80	Urine of night, sp. gr. 1026	11·25 „ „
Case of typhoid (female), 2 weeks' history of pyrexia. Temperature 101°—102°. Pulse 100—120	Urine of night, sp. gr. 1015	7·61 „ „

THE ACTION OF SALINE PURGATIVES.

By

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AND

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Over fifty years ago Buchheim[1] and H. Wagner[2] independently came to the conclusion that saline purgatives owed their power to the fact that they were only slowly and incompletely absorbed in the stomach and intestines. The water of solution, whether· taken with the salt by mouth or attracted by osmosis into the intestine, was believed to pass to the colon, where it produced fluid stools, which still contained the greater part of the salt.

A different theory was proposed by Aubert[3] about the same time. He injected five ounces of magnesium sulphate into a horse's vein and found that its bowels were opened soon afterwards. From this single inconclusive experiment he was led to suggest that saline purgatives act only after absorption, the effect depending on a specific irritation of the intestinal nerves leading to increased peristalsis. Numerous experiments performed by Buchheim, Wagner, Hay, Leubuscher and others seemed to show, however, that the intravenous injection of saline purgatives did not produce purgation, so that Buchheim and Wagner's theory held the field until a few years ago.

In 1901 Loeb observed that salts, which act as purgatives, also increase the irritability of skeletal muscle and nerve. At his suggestion J. B. MacCallum[4] reinvestigated the subject and came to the same conclusion as Aubert, viz., that the

saline purgatives only act after absorption, as he found that they produced their effect more rapidly after intravenous injection or direct application to the peritoneal surface of the intestines than after injection into the lumen of the gut. His experiments led him to believe that they act by directly stimulating both peristalsis and intestinal secretion. The experiments of Moreau, Brunton and Hay had shown that the fluid, which collects in the intestines after the administration of a saline purge, is succus entericus and not a mere exudation, thus confirming the idea that it is produced by a stimulation of the secretory nerves and not by any purely physical process such as osmosis.

MacCallum's views have not, however, been generally accepted. It has even been stated that intravenous injection of sodium sulphate produces constipation rather than diarrhoea.

Our observations by means of X-rays and auscultation on the passage of food along the alimentary canal of man[5] have shown that the cæcum is normally reached about four hours after a meal. Saline aperients may produce an action of the bowels within half an hour of their administration, and they rarely require as long a period as three hours. Hence it is difficult to understand how they can reach the colon by way of the alimentary canal with sufficient rapidity to act from the intestinal lumen, as they are supposed to do according to the commonly accepted theory of Buchheim and Wagner.

In order to investigate this question three individuals took two ounces of bismuth oxychloride in half a pint of cold water at 8 a.m. one morning. They breakfasted at 8.30 a.m. The cæcal sounds and the shadow of the cæcum were first observed at the normal time—about four hours after the meal. Hence the cold water, though taken half an hour before breakfast, did not reach the cæcum very rapidly, although it probably passed out of the stomach without delay. Probably it was completely absorbed from the small intestine, the bismuth being subsequently carried on by the remnants of the breakfast.

A few days later a Seidlitz powder was taken by the same individuals with two ounces of bismuth oxychloride and half a pint of water at 8 a.m., half an hour before breakfast. Once

more the cæcal shadow did not appear before the normal time, although some cæcal sounds could be heard at a slightly earlier period. The bowels had been opened normally before breakfast, and a fluid motion, the result of the saline purgative, was produced at 9.15, 9.40 and 9.45 respectively in the three individuals— that is to say, about three hours before the first trace of bismuth reached the cæcum and some time before the first cæcal sounds were heard. It might be suggested that the soluble saline purgative traverses the intestines more rapidly than the heavy and insoluble bismuth oxychloride, in which case the first appearance of the cæcal shadow would give no accurate indication as to the time of arrival of the purgative salt in the cæcum. We have, however, proved by observations on two patients, in whom fæces escaped from a fistula of the ileum, situated within a foot of the cæcum, that bismuth and purgative salts, when given together, travel at the same rate, both making a first appearance at the same interval after they were taken, and the quantity of each present in the fæces reaching a maximum at the same time. Hence it appears that some of the purgative salt must have been absorbed from the stomach or small intestine into the blood, from which it acted directly on the neuro-muscular mechanism of the colon, producing increased motor and scretory activity in the way described by MacCallum. The increased activity is apparently confined to the colon, though perhaps the slightly earlier occurrence of cæcal sounds, when the salt was taken, was due to the production of a secretion in the small intestine, which reached the cæcum in advance of the bismuth and the part of the aperient salt which was still unabsorbed.

We have further proved the correctness of Aubert's and MacCallum's theory by a completely different method, in which the fæces and urine were analysed after sodium sulphate had been given, and the results were compared with control analyses made on the previous day. The soluble sulphates were extracted and weighed as barium sulphate, and the equivalent amounts of SO_4 and of crystallised sodium sulphate were calculated.* It

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* Similar observations were made with identical results with magnesium sulphate.

was found that the watery stool, passed one or two hours after a drachm of sodium sulphate had been taken in half a pint of water, contained only a few grains more of the salt than the normal solid stool which had been passed earlier in the morning, immediately before the salt had been taken. The largest quantity of water which the salt present in the fæces could have held in the lumen of the gut so as to bring the osmotic pressure down to the level of that of the body fluids, was less than one-third of the amount of water actually present in the stool. It is thus clear that the excess of water present in the stool must have been actively secreted, as it could not have been attracted into the lumen of the gut by physical means alone. No more fæces were excreted until the next morning, when a normal solid stool was passed. The excess of sodium sulphate present in this stool over that present in the normal stools was four times as great as the excess in the watery stool passed an hour and three-quarters after the salt was taken. As the stool was quite solid, the presence of a purgative salt in the lumen of the lower part of the large intestine is clearly insufficient to produce a watery stool, as it should do if its purgative action depended on osmotic attraction. As the sodium sulphate did not act from the lumen of the gut, it must have acted from the blood. The slight increase in the quantity of sodium sulphate present in the watery stool cannot, as the bismuth observations show, have been due to the direct passage of the salt from the stomach along the alimentary canal to the rectum. It was doubtless partly due to the increased quantity of succus entericus secreted, as the latter normally contains sodium salts and sulphates. But the greater part of the excess was probably a result of the excretion into the lower end of the colon of some of the sodium sulphate absorbed from the upper part of the small intestine.

A comparison between analyses of the urine passed on the day on which the sodium sulphate was taken and that passed on the previous day showed that there was already a great increase in the percentage and still more in the absolute quantity of the total sulphates present in the urine in the four hours following the administration of the salt, and this was even more marked in the

subsequent four hours. These observations show that an increased quantity must already at this period have been circulating in the blood.

If the physical theory of the action of saline purgatives were correct, it would be difficult to understand how in some individuals they invariably fail to act. Observations made by us on a healthy man, on whom one drachm of magnesium sulphate had no effect, showed that a large proportion of the salt was present in a solid stool passed fourteen hours after it was taken. According to the physical theory it is difficult to understand why excess of water should not have been present in the stool. It is well known, however, that considerable variations occur among different individuals in their power of absorbing inorganic salts. In such cases as this, there seems to be a deficient absorption of the salt, so that no aperient action is produced. It passed through the intestines with the food, and some of it appeared in the first stool passed more than twelve hours after its administration, twelve hours being approximately the shortest period which our X-ray observations have shown is required for the normal passage through the intestines. In other individuals the power of absorption may be unimpaired, but the neuro-muscular mechanism of the intestine may be less responsive to chemical stimulation than is usually the case.

The chief argument against the view that saline purgatives only act after absorption is that intravenous injection of even larger doses than are required when given by mouth produce no purgation in animals. The probable explanation is that a continuous stimulation, such as is produced when small quantities are being constantly absorbed from the intestines over a period of two or three hours, is required; when the salt is injected all at one time into a vein it is rapidly excreted by the kidneys and bowels, so that its action is of insufficient duration for purgation to occur. Moreover, Barcroft[6] has shown that the failure of Hay, and others, to obtain purgation on intravenous injection of saline purgatives was due to the solutions used being too concentrated. He has also shown that the observations of certain other critics are fallacious, as they did not keep adequate controls, and only

used the milder purgatives mentioned by MacCallum. Only by accurate comparisons with control animals over short periods can the increase in the amount of fæces excreted, when sodium citrate or sulphate is injected subcutaneously or intravenously, be recognised, as the dose required to produce obviously watery stools is so great in rabbits that death generally results.

In our researches on the normal movements of the alimentary canal,[5] we showed that in defæcation the whole colon takes an active part, and that all the intestinal contents below the splenic flexure are excreted. In spite of the peristaltic activity of the cæcum, ascending colon and transverse colon, these parts are not completely evacuated (fig. 1), although a certain proportion of their contents is propelled further along the intestine. When, however, a dose of a saline purgative, sufficient to produce a single copious and semi-liquid stool, is given, the whole of the large intestine from the cæcum to the rectum may be completely emptied. This was well shown in an individual, who had taken two ounces of bismuth oxychloride with bread and milk at midnight, so that at 9 o'clock the following morning the shadows of the cæcum, ascending colon, transverse colon and descending colon were distinctly visible with the fluorescent screen (fig. 2). A drachm of magnesium sulphate in half a pint of water was then drunk, and soon afterwards breakfast was taken. The breakfast was found as usual to have produced a slight advance in the most forward part of the shadow, but there was otherwise no change in it. Half an hour later the aperient acted, a copious semi-fluid stool being passed. Every trace of a shadow had now disappeared, the cæcum being as completely emptied as the pelvic colon.

The X-ray observations already described, and others made in cases of constipation, have shown that saline purgatives produce little or no acceleration in the passage of the chyme along the small intestine, the colon being the part of the bowel upon which the salt present in the blood-stream acts most strongly. More-over, in two cases of fistula of the end of the ileum we found that a bismuth salt was excreted at the same interval after it was

taken, whether it was mixed with a drachm of sodium sulphate or not.

The recently published researches of Ury[7] show, however, that when large doses of magnesium sulphate (between a half and one ounce) are taken, peristalsis and secretion are increased in the small as well as in the large intestines, as a considerable proportion (46 to 77 per cent.) of the salt is found in the watery stool passed about an hour after its administration. This does not prove, as Ury believes, that it must act from the lumen of the bowel and not from the blood, as his own observations show that there is excess of the salt present ·in the blood and urine under these conditions.

Fig. 1.
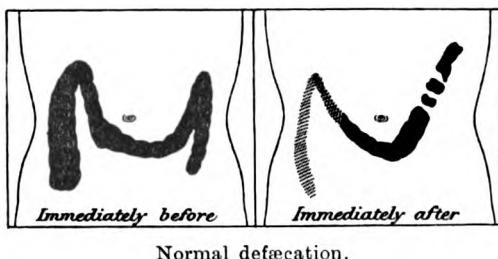
Normal defæcation.

Fig. 2.
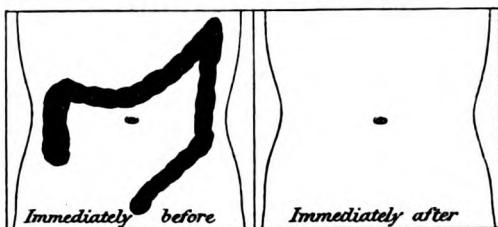
Defæcation following administration of 1 drachm of magnesium sulphate.

Thus saline aperients are particularly valuable when it is desired to produce a complete evacuation of the colon without interfering with digestion in the small intestine. They have the advantage in such cases over many vegetable purgatives, such as cascara sagrada and castor oil, in producing no acceleration in

the passage of the chyme through the small intestine, which would lead to diminished digestion by the pancreatic and intestinal juices; for X-ray observations made in ordinary cases of constipation, in which the colon is alone involved, and in one due to lead poisoning, in which delay occurs in the small as well as the large intestine, showed that cascara produces increased activity of all parts of the intestines,[8] and the same fact was recently observed in the case of castor oil by Magnus[9] in his experiments on cats. On the other hand, he found that senna acted on the large intestine only.

It is still necessary to show how the revived theory of Aubert and MacCallum of the action of saline purgatives can explain various points in connection with the ordinary methods used in their administration. They are most active when given dissolved in a considerable volume of water, because, as the experiments of Otto[10] have shown, solutions of salts are retained in the stomach until they become isotonic with the body fluids by dilution with the secretion of the gastric mucous membrane. Thus the nearer the solution of the salt is to being isotonic with the blood-plasma, the more rapidly it will pass into the small intestine, from which

FIG. 3.
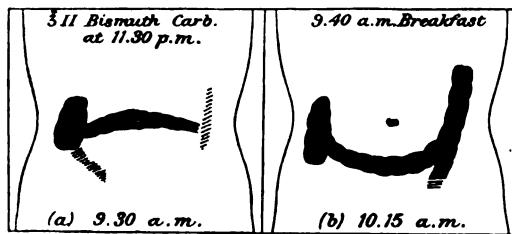
Effect of breakfast : (i) emptying of small intestine, (ii) advance in colon, (iii) lower position of transverse colon.

its absorption occurs. It is best given on an empty stomach, as it then passes directly into the small intestine ; on the other hand, if food is present in the stomach the salt passes slowly out with the food, so that it may be excreted almost as rapidly as it is absorbed ; the result is that no purgative action is produced,

but disturbances in gastric digestion often occur, owing to the abnormality in the secretion of gastric juice and the inhibition of ferment action to which it might give rise. Lastly, a saline aperient is best taken a short time before breakfast, because then the specific action of the salt is augmented by the normal stimuli, which cause the early morning to be the best time to open the bowels. The chief of these is breakfast, as our X-ray observations have proved that food taken on an empty stomach is the most powerful of all stimulants of movements of the colon (fig. 3). The importance of this factor is shown by the observation that in one individual a drachm of magnesium sulphate taken before breakfast produced an evacuation in thirty-five minutes, whereas the same dose given another morning, when no breakfast was taken, required seventy minutes to produce its action.

We are indebted to Mr. G. Marshall and Mr. G. E. Genge-Andrews for valuable assistance in several of the experiments.

TYPICAL ANALYSIS.

(F. Cook.)

2nd December, 1908 :—

Breakfast, 8.15 a.m.
Fæces passed, 8.30 a.m.

Fresh fæces	...	32·28 grms.
Dried fæces	...	15·72 grms.
Water	...	**80·9 per cent.**
Total SO_4 ...	...	0·0375 grms.
SO_4 in fresh fæces	...	**0·045 per cent.**
SO_4 in dried fæces	...	**0·238 per cent.**

Urine secreted between 8 a.m. and 12 noon, 250 cc., S.G. 1017.

Total SO_4 ...	...	0·386 grm.
Ethereal SO_4	...	0·045 grm.
Inorganic SO_4	...	**0·341 grm.**

Urine secreted between 12 noon and 4 p.m., 350 cc., S.G. 1014.

Total SO_4 ...	...	0·496 grm.
Ethereal SO_4	...	0·049 grm.
Inorganic SO_4	...	**0·447 grm.**

3rd December, 1908 :—

> Sodium sulphate 3·89 grms. (= 1 drachm), taken at 9.40 a.m. Break-
> fast at 10 a.m.
>
> Normal stool passed at 10.15 a.m.

Fresh fæces	...	49·75 grms.
Dried fæces	...	9·95 grms.
Water	...	**80·0 per cent.**
Total SO_4 ...	...	0·016 grm.
SO_4 in fresh fæces	...	**0·032 per cent.**
SO_4 in dried fæces	...	**0·161 per cent.**

> Watery stool (the result of the purgative) passed at 11.25 a.m.

Fresh fæces	...	220·10 grms.
Dried fæces	...	19·64 grms.
Water	...	**91·07 grms.**
Total SO_4 ...	...	0·091 grm.
SO_4 in fresh fæces	...	**0·041 per cent.**
SO_4 in dried fæces	...	**0·465 per cent.**

> Urine secreted between 9.40 a.m. and 1.40 p.m., 200 cc., S.G. 1026.

Total SO_4 ...	...	0·720 grm.
Ethereal SO_4	...	0·095 grm.
Inorganic SO_4	...	**0·625 grm.**

> Urine secreted between 1.40 p.m. and 5.40 p.m., 225 cc., S.G. 1025.

Total SO_4 ...	...	0·857 grm.
Ethereal SO_4	...	0·069 grm.
Inorganic SO_4	...	**0·788 grm.**

4th December, 1908 :—

> Normal stool passed 8 p.m.

Fresh fæces	...	123·04 grms.
Dried fæces	...	27·92 grms.
Water	...	**77·3 per cent.**
Total SO_4 ...	...	0·270 grm.
SO_4 in fresh fæces	...	**0·220 per cent.**
SO_4 in dried fæces	...	**0·968 per cent.**

SUMMARY.

	Grams.	Per cent. in fresh fæces.	Per cent. in dried fæces.
Excess of SO_4 in watery stool (3rd December, 1908) over average of two normal stools $\Big\{$	0.065 $= 0.215$ cryst. $Na_2 SO_4$ $\Big\}$	0.003	0.266
Excess of SO_4 in normal stool of next day (4th Dec., 1908) over average of two normal stools $\Big\{$	0.244 $= 0.812$ cryst. $Na_2 SO_4$ $\Big\}$	0.181	0.769
Excess of inorganic SO_4 in urine passed in first four hours following administration $\Big\{$	0.283 $= 0.945$ cryst. $Na_2 SO_4$ $\Big\}$		
Excess of inorganic SO_4 in urine passed in second four hours following administration $\Big\{$	0.340 $= 1.135$ cryst. $Na_2 SO_4$ $\Big\}$		

Hence, of the 3.89 grm. of Sod. Sulphate taken at 9.40 a.m. on 3rd December, 1908—

0.21 grm. were excreted in the watery stool $1\frac{3}{4}$ hours later.

0.81 grm. were excreted in the normal stool passed the next day.

0.945 grm. were excreted in the urine passed in first 4 hours following its administration.

1.135 grm. were excreted in the urine passed in second 4 hours following its administration.

0.79 grm. were passed subsequently in the urine or fæces.

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OBSERVATIONS ON THE CHANGES IN THE BLOOD AND BONE MARROW PRODUCED BY EXPERIMENTAL ANILINE POISONING.

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WE propose to give here an account of a number of observations on the changes in the blood and bone marrow of rabbits suffering from experimental poisoning with aniline. In all cases the aniline has been given as such, either undiluted or in the form of a 2 per cent. solution in 0·8 per cent. salt solution. The salts of aniline, such as the hydrochloride, should be avoided, since they are to all intents and purposes nothing but aniline dissolved in acids, and the effects of the aniline are likely to be, and in fact we have found them to be, complicated by the influence of the mineral acid.

It is well known that aniline, dinitrobenzene, and similar bodies produce profound effects on the red corpuscles and hæmoglobin, and the ill-effects of these substances are no doubt in part due to the blood changes. Deprivation of oxygen to a greater or less degree is caused by the destruction of hæmoglobin. Other severe and often fatal symptoms are apparently due to the disintegration of red corpuscles; intravascular hæmolysis,

whether occurring naturally, as in paroxysmal hæmoglobinuria, or produced experimentally in any way, is commonly associated with acute illness, and sometimes death, the immediate causes of which require further elucidation. Aniline, however, is evidently pretty poisonous, quite apart from its effects on the blood. Sudden death not infrequently follows its administration to rabbits by subcutaneous or intravenous injection. Aniline oil, injected intravenously as such, naturally kills by causing pulmonary embolism. A dose of 0.2 cc. dissolved in 10 cc. of salt solution and given intravenously is, in our experience, always immediately fatal to a moderate-sized rabbit (1500 to 2000 grammes), without producing any changes in the blood or anything (such as general thrombosis) which can be discovered post-mortem to account for death. Most rabbits show very few or no symptoms after 0·1 cc. aniline in salt solution intravenously, and this dose may be repeated at least six times at intervals of an hour without causing severe illness. Given subcutaneously, aniline is much less poisonous ; 1 cc. is seldom fatal, and some animals survive 2 cc.; 0·2 cc. may even produce no discernible changes in the blood. There is, however, great individual variability ; thus, of one group of five animals (1590 to 1770 grammes body weight) which received 2 cc. each subcutaneously, one died within five minutes with convulsions, two died in the night (*i.e.*, within twenty hours), and the other two lived, showing extensive changes in their blood. The immediate symptoms take the form of prostration, panting, convulsions, and sometimes loss of consciousness. If not fatal, they commonly disappear completely within twenty-four hours, and do not again recur. In one instance, however, a rabbit of 1260 grammes received 1 cc. aniline subcutaneously ; an hour later it was completely prostrate and unconscious, with intermittent convulsive seizures, and for five hours it seemed like to die. Some improvement then appeared, but the next day it was completely paralysed in its hind legs, and seemed very ill. The next day, however, it was completely well and so continued, at no time showing any marked changes in its blood.

We have, however, not been concerned in detail with the poisonous effects of aniline on tissues other than the blood ; the fact that it exerts a direct and very toxic action on other organs, presumably the central nervous system in particular, is, however, sufficiently obvious. The symptoms shown by persons engaged industrially with aniline are altogether out of proportion to, and can hardly be caused by, the changes found in their blood.[1]

1.—CHANGES IN THE TOTAL AMOUNT OF HÆMOGLOBIN AND THE VOLUME OF THE BLOOD.

In conjunction with C. G. Douglas, we have followed over a period of ten weeks the changes in the total amount of hæmoglobin and in the volume of the blood by the carbon monoxide method[2] in a severe case of aniline poisoning in a rabbit. The results were, shortly, as follows :—

Date.	Body weight, grammes.	Hæmoglobin, per cent.	Total hæmoglobin in cc. of oxygen capacity.	Volume of blood cc.	Treatment.
March 26	3120	65	19·5	163	
„ 28	3250	59	21·2	195	
„ 30	3020	71	20·9	158	0·2 cc. intraperitoneally.
„ 31	2970	63	—	—	„ „
April 1	3020	67	—	—	„ subcutaneously.
„ 2	2970	69	17·5	137	„ intraperitoneally.
„ 3	2950	67	—	—	„ „
„ 4	3000	60	19·6	175	„ „
„ 6	3150	60	—	—	2·0 cc. subcutaneously.
„ 8	2980	31	13·4	217	
„ 10	2900	15	10·1	360	
„ 13	2820	20·5	10·5	276	
„ 24	2450	35	10·6	163	
„ 28	2240	32	10·0	169	
May 4	2260	34	9·8	155	
„ 11	2230	38	14·2	200	
„ 20	2300	50	15·2	164	
„ 29	2680	61	19·8	175	

The chief result of this experiment which we would emphasize is that the readings of the hæmoglobinometer do not represent

[1] See, *e.g.*, Malden, Journal of Hygiene, vol. vii. (1907), p. 672.
[2] Journal of Pathology and Bacteriology. Vol. xiii. (1909), p. 256.

the actual total amount of hæmoglobin in the blood.   The direct determinations by the carbon monoxide method show that almost exactly 50 per cent. of the total hæmoglobin was destroyed, while the hæmoglobinometer value fell from 65 to 15, implying a destruction of 77 per cent.   Note, too, that over the period April 10th to May 4th the total hæmoglobin actually remained the same, though the hæmoglobinometer suggested that during that period it had more than doubled.   This lack of correspondence is due to the fact that during the early days of the acute blood destruction which followed the dose of 2 cc. of aniline the volume of the blood was much increased, from 170 cc. to as much as 360 cc.   Subsequently the volume was restored to normal without any increase of total hæmoglobin ; this concentration put up the hæmoglobinometer value from 15 to 35. Regeneration of hæmoglobin did not begin to exceed destruction till a month after the last dose of aniline ; after that the normal amount was reached fairly quickly, and the animal lived for some time in perfect health.

2.—Optical Changes in the Blood.

a. Considerable difficulty may be met with in doing the titrations necessary for the determination of the total and percentage oxygen capacity of the blood by a *turbidity* varying from a slight opalescence to a high degree of muddiness.   This condition is only seen in severe cases.   It cannot be cleared up by alkalis or filtration, nor by centrifugalisation within the limits of speed at our disposal.   It is no doubt partly due to fragmented red cells (see below), possibly in part to the considerable leucocytosis which is generally present, but it seems clear that some of it is caused by particles which are not apparent on any ordinary method of microscopical examination.   Their nature remains to be determined.

b. A substance appears in the blood which may be described as yellow or brown, according to its concentration ; it has no spectroscopic characters which can be disentangled from those of the accompanying hæmoglobin.   In exaggerated cases this brown colour is obvious at once, or on simply diluting the blood ;

in mild cases, however, it is only apparent when the blood is diluted, saturated with carbon monoxide, and compared with normal blood similarly treated. This is an extremely delicate method for detecting the presence of traces of many abnormal pigments in the presence of an excess of hæmoglobin.[3]

c. A second abnormal pigment also appears in the blood, which shows, on spectroscopic examination, a band in the red which superficially resembles the most visible band of acid or neutral methæmoglobin. It is, however, clear at once that this substance is not the methæmoglobin which is described in the blood of rabbits poisoned with aniline by, *e.g.*, Malden (*loc. cit.* p. 682), since the band remains unaltered on adding reducing agents. Closer examination also shows that the position of the band differs in the two cases. With the scale of the spectroscope so adjusted that the redward edges of the redward absorption bands of oxyhæmoglobin and carbon monoxide hæmoglobin lie at 593 and 589 respectively, the aniline band extends 620–625, and the ferricyanide methæmoglobin band is at 625–635, the band of alkaline methæmoglobin being at 600–610. On adding ferricyanide to blood showing the aniline band, the latter immediately disappears. Saturation with carbon monoxide shifts the aniline band bluewards to 610–618.

The "brown substance" and the "band substance" are not the same. It has been repeatedly observed that the blood may be very brown without showing the characteristic band in the red which we have described. This happens especially during the more advanced stages of blood destruction, and the band often disappears as the brownness increases. But it seems probable that the "band substance" is also brown or yellow, since we have never seen the band in blood which did not also show an abnormal degree of yellowness on saturation with carbon monoxide.

An advanced degree of brownness is generally associated with much histological alteration in the red corpuscles, and under

[3] Allowance must of course be made for the fact that normal rabbit's blood often contains a trace of some unknown substance which prevents the full pink tint of normal human blood being attained by saturation with carbon monoxide.

these circumstances the plasma of citrated blood is yellow and may show the band in the red. The blood may, however, show the band to a marked degree, and to some extent be brown, in the complete absence of any morphological changes in the red cells, and it can then be shown that the " band substance " is contained entirely within the corpuscles. That the " brown substance " without absorption bands may be altogether within the corpuscles is probable, but it cannot be definitely affirmed. The samples which we have examined with clear plasma have all shown the band, and the associated brownness may be due to this substance rather than to the " brown substance."

The exact nature of both these substances is extremely obscure. We have been unable to separate either of them from the hæmoglobin. The " band substance " never seems to occur in anything but small amounts. It accompanies the earlier rather than the more advanced stages of aniline poisoning, and the effect of carbon monoxide and ferricyanide suggests that it is something not far removed from hæmoglobin. On the other hand, it may not be a derivative of hæmoglobin at all.

This state of affairs is distinctly different from that found in human cases of aniline poisoning. In some of these, at any rate, there is no doubt that the brown pigment present is really methæmoglobin. Such was the case in the only instance of human poisoning which we have had an opportunity of examining.[4] In other cases, however, the fact has been noted that the band in the red did not disappear on the addition of reducing agents.

3.—Changes in the Histology of the Blood.

The hæmal *leucocytes* have not been studied in much detail, partly owing to the notorious unsuitability of rabbits for the purpose. We have, however, noted that aniline poisoning is, in

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[4] A man having drunk a few ounces of a dilute solution of some salt of aniline was admitted to Guy's Hospital, under the care of Dr. Hertz. Six hours after taking the aniline he was very blue, unconscious, and seemed moribund. His blood was very brown and showed a plain band in the red, which corresponded in all respects with that of methæmoglobin. The next day the band could not be seen, and only a faint yellow tint could be detected after saturation with CO. The next day he was practically well. There were no histological changes in the red cells.

its early stages, regularly accompanied by a leucocytosis which may reach the value of 30,000 to 40,000 per cubic millimetre. The increase may be due either to polynuclear cells or to the lymphocytes. In one of Malden's (*loc. cit.*, p. 680) experiments there was a considerable increase in the proportion of large mononuclears after the first few days, and we have noticed the same thing. This may be of interest as indicating a response to the products of the disintegration of red cells.

More definite and characteristic changes are found in the *red corpuscles*. In an advanced case, on the third or fourth day after a single large dose (1 or 2 cc. subcutaneously) of aniline, when the blood is found to be highly turbid and muddy on dilution, and quite brown in colour, the signs of red cell destruction are very marked. Large numbers of fragments of red cells are found, some circular in outline, some more irregular, and staining with Jenner's stain much the same as normal corpuscles. Besides these, and probably leading up to them, we have noted a very peculiar appearance, and one which we have not seen in a varied experience of different blood conditions in rabbits.[5] Projecting from otherwise normal cells are small nipple-like projections, which may be conveniently called "blobs" (see Fig. 2). Without prejudice to the question of how many (if any) skins, envelopes, differentiated outer layers, membranes, or cuticles a red cell may possess,[6] these blobs look as if an outer skin had split and that some of the contents, contained in a second skin, had been herniated through the opening. The contents, which stain deeply, tend to be aggregated towards the free extremity of the blob, and it seems pretty clear that they become detached to form some of the fragments of red cells already mentioned. In the interval between the deeply-stained extremity and the

[5] It is possible that they are the same as the " bud-like projections " mentioned by Hunter (Pernicious Anæmia, 1901, pp. 174–6), as occurring in rabbits after the injection of distilled water or pyrogallic acid. We have not seen them in these conditions.

[6] An admirable account of some fundamental observations relating to the membrane of red cells will be found in the Guy's Hospital Reports, No. xiii. (1841), p. 379, by G. O. Rees and S. Lane.

periphery of the parent red cell, rendered concave at the point of attachment by the gap in the outer skin, the inner skin may be distinctly seen.

Polychromasic red cells are abundant in the blood after the first forty-eight hours. Nucleated red cells also occur in moderate numbers. These two last abnormalities,[7] together with the marked variation in size which appears with them, are to be distinctly separated from the blobs and fragmentation. The latter are signs of blood destruction, the former of the active regeneration of new red cells to replace those which have been disintegrated. It is not without interest that we have never seen signs of destruction in these new cells.

These changes in the minute anatomy of the red cells, like the changes in the pigments, do not reach their maximum till the third or fourth day after the subcutaneous injection of a large dose. The two phenomena do not, however, run exactly parallel. The fact that the abnormal pigment with a band in the red part of the spectrum is, in the early stages of poisoning, confined entirely within the corpuscles, has already been noted, and at this point no morphological aleration in the red cells can be detected. A faint, but definite, yellow tinge can be detected for the first time seven hours after the subcutaneous injection of 1 cc. aniline in a 1500-gramme rabbit. The band cannot usually be seen till next day, possibly because the tint of the diluted blood saturated with coal-gas shows smaller traces of the abnormal pigment than can be detected with the spectroscope. Blobs, which constitute the earliest histological change, have never been found less than twenty hours and often not before forty-eight hours, by which time the pigmentary change is far advanced. In very mild cases (*e.g.*, 0.1 cc. in salt solution subcutaneously) the only histological change in the blood may be some polychromasia and a slight increase in nucleated reds. These signs of regeneration may be found when even the changes in the pigments have been so slight as to be recorded as doubtful.

[7] Some polychromasic red cells occur in the blood of normal rabbits, especially in young animals.

4.—MECHANISM OF THE DESTRUCTION OF RED CELLS.

The characteristic changes in the pigment and red cells which have been described cannot be produced by the action of aniline *in vitro.* The presumption is, therefore, that they are not caused by aniline itself, but by some decomposition product arising within the body. We have been unable to produce them by incubating together mashes of the different organs of rabbits with blood and aniline, nor by incubating the bodies of rabbits which have died very soon after a large intravenous dose. But the pigment changes, at any rate, may sometimes be obtained locally in two to four hours by injecting subcutaneously in rabbits a mixture of blood and aniline. That the action is not direct upon the blood is confirmed by the observation that the changes are not very much accelerated by injecting aniline intravenously instead of subcutaneously. As already mentioned, intravenous doses must be small, but they may be repeated fairly frequently to an amount far beyond the dose fatal at one injection. Two similar rabbits were treated in parallel with a 2 per cent. solution of aniline in salt solution; of this A received intravenously 5 cc. at 9.40, 10.30, 11.50, and 2.10, and 10 cc. at 3.30 and 4.30 (in all 0·8 cc. aniline); B had the same doses at the same times subcutaneously; in both the blood was examined at frequent intervals. In A a brown tint was first seen at 3.30, with a doubtful band in the red, and at 4.30 the blood was definitely brown and the band well marked. In B no change was found till 4·30, when the blood was slightly brown and the band doubtful. In A blobs first appeared on the second day after, in B not till the third day after; in both they disappeared again on the seventh day, when the blood was almost normal. In A the percentage of hæmoglobin fell from 74 to 46, in B from 78 to 54.

5.—CHANGES IN THE BONE MARROW.

The destructive changes in the blood are not represented in the bone marrow; we find here the signs of reparation which, in the blood, is represented by polychromasia, punctate basophilia, nucleated red cells, and abnormally-sized, especially abnormally large, pale red corpuscles. The proportion in which these

different signs of regeneration are present in the blood in rabbits
varies a great deal with the cause of the precedent blood destruc-
tion. Perhaps the most noticeable feature on this point in
aniline poisoning is the comparative infrequence of nucleated red
cells; they are equally uncommon in rabbits in post-hæmorrhagic
anæmia, and contrastingly abundant in phenylhydrazine
poisoning. Their relative rarity indicates the absence of undue
precipitancy in turning red cells out of the marrow into the blood,
though a considerable degree of haste in the process is shown by
the abundance of polychromasic cells. The regenerative changes
in the blood follow very quickly on the destructive changes;
indeed, if only infrequent examinations are made, the two
processes may appear to be actually simultaneous. The reaction
is very prompt, and, as mentioned above, very delicate, as it may
be found when the signs of destruction have escaped notice. The
existence of some leucocytosis must also be considered in relation
to the findings in the bone marrow.

The method of examination by means of glycerine films has
already been described by one of us (C. P. J.).[8] A small piece of
fresh marrow from the shaft of the femur is gently dissociated,
conveniently by stirring with a platinum loop, in a neutralised
10 per cent. solution of glycerine; a loopful of the emulsion is
gently spread on a clean cover-glass, and the film allowed to dry
at room temperature till it has a ground glass appearance. It is
then stained in the ordinary way with Jenner's stain.[9]

In such films the individual cells lie well separated from one
another, and can be studied to advantage. Differential counts
are readily made, premising that the ordinary difficulties of
grouping cells which represent different stages of development of
an organ, and hence pass insensibly from one group to another,
will not be absent. In the marrow of normal rabbits of about
1,500 to 2,000 grammes in weight, the different marrow cells may
be grouped as follows (see fig. 1 and key) :—

[8] British Medical Journal, 1905, i, p. 409; see also *ibid.*, October 28th, 1905.
[9] 0.75 gram Grübler's dry stain in 100 cc. Merck's methyl alcohol gives a
uniform and reliable preparation.
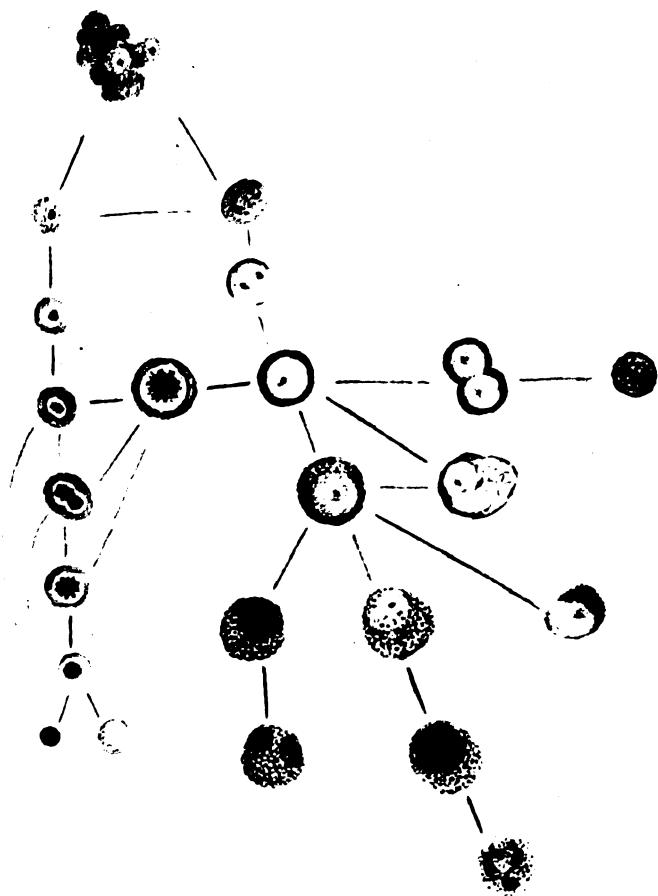
FIG 1.

FIG. 2.

KEY TO FIGURE I.
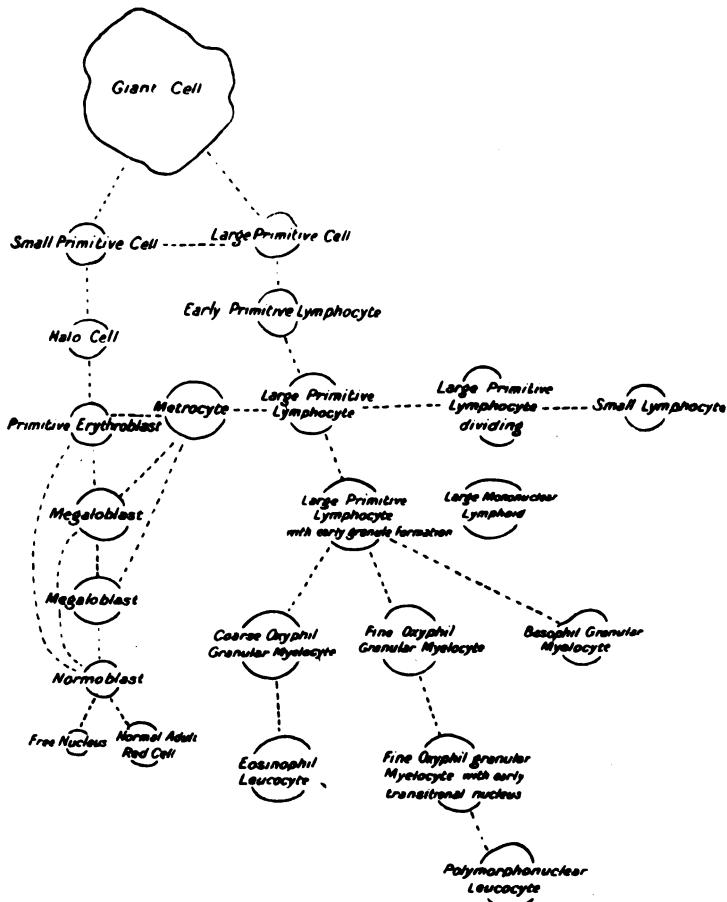
A.—Giant Cells.

The origin and fate of the giant cells is undetermined ; there are, however, reasons for supposing that some of the nuclear bodies become detached as primitive lymphoid cells. Owing to their more intimate attachment to the reticulum, and to their large size, the proportionate number found in marrow films probably represents less than their actual abundance.

B.—Lymphoid Cells.

1. *Small primitive cells* occur invariably in the bone marrow of different animal types ; they appear as blue homogeneous discs, 3 to 7 μ in diameter, containing one or more deeply-stained nucleoli, but without an obvious nucleus or cell wall.

2. *Halo cells* differ from small primitive cells by the development of an unstained peri-nucleolar area ; they constitute the prestages of the primitive erythroblast.

3. *Large primitive cells*, like the small primitive cells, but larger (up to 10 or 12 μ in diameter), often oval, and with two or more nucleoli.

4. *Large primitive lymphocytes*, or " non-granular myelocytes." These are developed from the preceding by the differentiation of a deep basophil ring, at first on one side of and later all round the apparent cell, which now becomes an obvious nucleus. These cells are frequently seen in process of division, producing two smaller cells of the same type. In vacuoles, in the dark, cytoplasm oxyphil granules may be seen, and we thus reach the earliest stage of development of granular myelocytes. From these large primitive lymphocytes also arise the small hæmal lymphocyte in its definitive form, and, at any rate under abnormal circumstances, where the need for red cells is great, the precursors of megaloblasts (metrocytes).

5. *Small lymphocytes* are derived directly from the preceding ; they are not abundant in the marrow.

6. *Large mononuclear lymphoids* (so-called " hyaline cells ") have a large nucleus, often ovoid or reniform in shape, and loosely

reticulate and granulous[10] cytoplasm. They are possibly derived from primitive lymphocytes, but appear to originate more commonly by the growth and degeneration of true lymphocytes. They only occur occasionally in bone marrow, and are probably derived from the circulating blood.

C.—LEUCOID CELLS.

1. *Fine granular oxyphil or neutrophil marrow cells* are very variable, representing as they do the gradation from the large primitive lymphocyte to the polymorphonuclear leucocyte. The granules first appear in the cytoplasm at the edge of the nucleus, and they increase in number as the nucleus becomes more irregular in shape, a process which begins before they have left the bone marrow. It is suggested that one purpose which is subserved by the acquisition of the contorted and irregular nucleus which is characteristic of the adult leucocyte is that the nuclear surface is thereby much increased, and the production of granules is thus facilitated.

2. *Coarse granular oxyphil or eosinophil marrow cells*, the precursors of the coarse granular eosinophile leucocyte.

3. *Basophil granular marrow cells*, the precursors of the basophile granular leucocyte (so-called " mast cell ").

4. *Polynuclear leucocytes* include fine oxyphile, coarse oxyphile, and basophil leucocytes, of which the former predominate.

D.—ERYTHROBLASTIC CELLS.

1. *Primitive erythroblasts* are extremely variable in appearance, and are often very difficult to differentiate from the halo cells from which they are derived. The typical cell may be described as a halo cell with a well-marked perinuclear ring surrounded by a pale pink or purple-stained marginal zone ; the nucleus is faintly basophil, and shows an indistinct nucleolus. Degenerate forms with vacuolated or irregularly stained and polychromasic cytoplasm are often seen.

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[10] By this we mean a condition of cytoplasm which, although holding no granular bodies in its reticulum, yet would be erroneously described as " hyaline."

2. *Metrocytes* are of the nature of large primitive erythroblasts. They are large cells, 15 to 20 μ or more in diameter, with round or irregular contours. The cytoplasm appears homogeneous, and usually stains deeply oxyphil, but is often polychromasic and of a purple or brown colour. The nucleus is large, and stains deeply in that peculiar tint of blue which is associated with the nuclei of red cells; it is usually surrounded by a narrow unstained area, and presents various states of activity and division. Metrocytes are only rarely met with in normal adult marrow, but they may be numerous during active regeneration (after hæmorrhage, aniline poisoning), and are abundant in embryonic marrow; as mentioned above, under these abnormal circumstances, they appear to arise from the primitive lymphocytes.

3. *Megaloblasts* may be regarded as the normal representatives of metrocytes in adult marrows in that they give rise to daughter cells, which develop into normoblasts.

4. *Normoblasts* are adult nucleated red cells, and in many animals are the final stage of red cell development. In marrow there are constantly found a number of these cells undergoing mitosis: these may be distinguished as prenormoblasts, and constitute the link between megaloblasts and normoblasts proper.

5. *Free red cell nuclei* occur in all marrow preparations. The evidence obtained from marrow films is entirely in favour of the view that normoblasts become red cells by extrusion of the nucleus as a whole—a process which may be called *karyoexiesis*—rather than by its disintegration and solution *in situ* (karyolysis). The fate of these free nuclei has not been made out; some are taken up by phagocytic cells, and they are often seen enclosed in giant cells.

In the marrow, therefore, one may distinguish three main groups of cells—(1) a primitive group—*lymphoid cells*—which give rise ultimately to both red cells and leucocytes; (2) a group —*leucoid cells*—which are definitely destined to form leucocytes and (3) a group of *nucleated red cells*, which are irrevocably on the way to become red corpuscles. A call for leucocytes in the

body, and an increase of leucocytes in the blood, is associated
with an increase of leucoid cells in the marrow. A necessity for
a more abundant supply of red cells in the blood is marked by a
great increase in the proportionate number of the nucleated red cell
group in the marrow. These are well-known facts. The point,
however, to which especial attention is directed is the increase in
the lymphoid series which accompanies active red cell regenera-
tion. The first response in the marrow to red cell destruction is
an increase in free nuclei (*i.e.*, non-nucleated red cells are
hurriedly turned out), then the nucleated red cells are found
more abundant, and later still the stages preparatory to nucleated
red cells (*i.e.*, the lymphoid series) show an increase.

In each differential count of marrow films, 500 lymphoid and
leucoid cells were enumerated and classified. The frequency of
each variety is expressed as a percentage of the total number
counted. The nucleated red cells are also noted during this
count, and their number is expressed in terms of their percentage
on the lymphoid and leucoid cells counted. Thus, in one count
of 500, 242 lymphoid cells and 258 leucoid cells were enumerated;
in going over this 500 cells, 81 nucleated red cells were found.
The result, therefore, was—lymphoids 48·4 per cent., leucoids
51·6 per cent., nucleated red cells 16·2 per cent.

The limitations of this method of differential counts are
sufficiently obvious. A proportionate increase in one kind of
cell necessarily involves an apparent diminution of other kinds,
and a rise in the percentage of, *e.g.*, leucoids, *may* be due to
either a real increase or to a diminution of lymphoids. This
error may be evaded by ascertaining the total absolute numbers
of the various kinds. In the case of the hæmal leucocytes it is
easy to determine the absolute number in one cubic millimetre,
and, by a determination of the blood volume, in the whole
circulating blood. Andrewes (Supplement to the Thirty-seventh
Report of the Local Government Board, Cd. 4634, 1909, p. 316)
has recently sought to apply the same idea to the enumeration of
the cellular constituents of marrow. By an ingenious method
he determines the absolute number in one cubic millimetre of
marrow. Apart from the fact that it takes no account of the

considerable variations which may—and in fact do—occur in the total mass of active marrow, and therefore does not necessarily give materially more accurate results than proportionate counts, this method would have been entirely inadmissible in the present inquiry, since it involves the study of the cells in paraffin sections.   In our experience it is quite impossible to make an adequate histological examination of bone marrow in specimens prepared by this method.   The cells are shrunken and crowded together, so that the finer details of their structure and staining reactions are much obscured.   Only a very coarse differentiation of the various kinds can be effected in this way.

The *proportionate frequency of the different kinds of cells in the marrow of normal rabbits* of 1500–2000 grammes body-weight is subject to some variations.   The following table summarises the figures obtained in eight animals :—

	Maximum.	Minimum.	Average.
A.—Giant cells ...	1·6	0·6	1·0
B.—Small primitive cells...	27·2	15·4	21·0
Halo cells ...	5·6	2·6	3·9
Large primitive cells...	6·8	2·8	4·5
Small lymphocytes ...	7·0	1·6	3·1
Large primitive lymphocytes ...	28·8	5·0	15·5
Large mononuclear lymphoids	1.6	0·0	0·6
C.—Fine oxyphil granular cells ...	49·0	33·8	42·2
Coarse oxyphil granular cells ...	2·6	0·0	1·5
Basophil granular cells	4·8	1·2	2·1
Polymorphonuclear leucocytes	14·0	0·2	4·5
D.—Primitive erythroblasts and metrocytes	3·6	0·0	1·6
Megaloblasts	4·2	1·8	3·0
Normoblasts	7·0	3·4	4·8
Free nuclei ...	10·4	2·8	6·2
Total lymphoid cells (B) ...	58·0	37·2	48·7
Total leucoid (C)...	61·8	40·4	50·4
Total nucleated red cells (D) ...	19·2	13·2	15·6

Of the marrow cells, therefore, about half are lymphoids and half leucoids.   Of the *lymphoids*, some two-fifths are small primitive cells, which may give rise either to red cells or leucocytes ; and about a third are large primitive lymphocytes (" nongranular myelocytes "), which normally develop into

polymorphonuclear leucocyte, but which may contribute to the erythroblastic series. Of the *leucoids* more than four-fifths are finely granular oxyphil cells, the precursors of the predominant leucocyte of the blood. The chief variation in the different marrows, here summarised, involves the large primitive lymphocytes; on further examination it appears that the smaller animals had distinctly more than the larger individuals. The four smaller rabbits averaged 22 per cent., the four larger ones only 9 per cent.; the figures for leucoids were 46 per cent. and 55 per cent. respectively, so that the difference is to some extent due to the fact that the larger animals had their cells in a further state of development than the smaller individuals.

Changes in the marrow in aniline poisoning.—We give here the details of the observations on five rabbits :—

Rabbit 4.—Female, 2040 grammes; 1 cc. aniline subcutaneously. The next day the blood was slightly brown when saturated with coal-gas; no band in the red; nothing abnormal histologically in blood-films; the animal was killed and the marrow examined at once, with the following result :—

Giant cells	1·0	
Small primitive cells	22·6	
Halo cells	10·2	Total
Large primitive cells	4·4	lymphoid
Small lymphocytes...	0·8	= 53·4 per cent.
Large primitive lymphocytes	15·0	
Large mononuclear lymphoids	0·4	
Fine oxyphil	27·6	Total
Coarse oxyphil	1·2	leucoids
Basophil	2·6	= 45·6 per cent.
Polynuclear leucocytes	14·2	
Primitive erythroblast	5·6	Total
Megaloblasts	2·6	nucleated
Normoblasts	3·6	red cells
Free nuclei	10·6	= 22·4 per cent.

Note the usual form of initial erythroblastic action, viz., increase in free nuclei; the marrow appears to have commenced action before any change could be detected in the cells in the blood. The proportion of polymorphonuclear leucocytes is high, but the animal had 60 per cent. of these in its blood.

Rabbit 3.—Female, 2240 grammes; 1 cc. anilin subcutaneously. Next day the blood was a little brown, and showed the band in the red; next day the same. The animal was killed, and the " band substance" found to be entirely within the corpuscles. No histological changes were found in the blood till the second day, when a few red cells showed appearances which, with some hesitation, were considered to be probably the early stages of " blobs.'' The marrow showed :—

Giant cells	...	...	...	...	0·2	
Small primitive cells		...	...	...	30·4	
Halo cells	...	...	...	...	6·0	
Large primitive cells		...	...	..	5·2	Total lymphoids = 54·2 per cent.
Small lymphocytes	...	...	...	...	1·8	
Large primitive lymphocytes		...	...	10·6		
Large mononuclear lymphoids		...	...	0·8		
Fine oxyphil	...	...	...	...	27·6	
Coarse oxyphil	...	...	...	...	2·4	Total leucoids = 45·0 per cent.
Basophil	...	...	...	...	3·4	
Polynuclear leucocytes		...	...	...	11·6	
Primitive erythroblasts		...	...	...	13·8	
Megaloblasts	...	...	...	...	12·2	Total nucleated red cells = 48·4 per cent.
Normoblasts	...	...	...	...	18·4	
Free nuclei	...	...	...	...	4·0	

Note the large increase of nucleated reds of all kinds. Many of the normoblasts were very immature and close to primitive erythroblasts. The small primitive cells are also increased.

Rabbit 2.—Male, 1650 grammes; 2 cc. analine subcutaneously. (Of two other rabbits which received the same dose with this animal, one—1670 grammes, male—died in convulsions in five minutes; the other—1770 grammes, male—died in the night.) The blood was rather opalescent on dilution and slightly brown, but with no band in the red, next day; on the second day the band was faintly visible, and the blood very cloudy and quite brown; on the third day the same, and the animal, which did not appear ill, and had increased in weight by 290 grammes, was killed. Blood films showed :—

	Differential Leucocyte Connt.					Nucleated red cells with 500 leucocytes.	Alterations in red cells.
	Lymphocytes.	Mononuclears.	Fine Oxyphiles.	Eosinophiles.	Basophiles.		
1st day	59·0	1·0	38·0	0·2	1·8	0	Normal.
2nd day	48·6	7·8	41·6	0·4	1·6	1	Many show blobs.
3rd day	68·8	8·2	20·0	0·2	2·8	12	Nearly all show blobs except the megalocytes, which are polychromasic.

The marrow films gave the following results : —

Giant cells ...	...	...	...	...	1·4	
Small primitive cells		...	...	...	26·0	
Halo cells ...	...	...	...	...	3·0	Total lymphoids = 61·4 per cent.
Large primitive cells		...	...	...	9·6	
Small lymphocytes ..	...	...	...	...	4·8	
Large primitive lymphocytes		...	...	16·8	
Large mononuclear lymphoids	...		...	...	0·6	
Fine oxyphil...	...	...	...	...	19·0	Total leucoids = 37·2 per cent.
Coarse oxyphil	...	...	...	...	2·0	
Basophil ...	...	..	...	...	2·0	
Polynuclear leucocytes	...	...	...	14·2	
Primitive erythroblasts	...	...	...	7·6	Total nucleated red cells = 32·2 per cent.
Megaloblasts...	...	...	...	...	9·0	
Normoblasts ...	...	...	...	...	3·0	
Free nuclei ...	...	...	...	...	12·6	

Note the active lymphoerythroblastic reaction.

Rabbit 1.—Female, 1620 grammes ; 2 cc. aniline subcutaneously. (A second rabbit—male, 1590 grammes—died in the night with the same treatment.) Next day the animal was ill, and the blood quite brown, with a band in the red ; the day following the blood was very brown and muddy, and on the next day the animal, which now weighed only 1370 grammes, was killed. There was considerable intravascular hæmolysis, and the citrated plasma was brown and showed the band in the red well,

though not so intensely as the blood in the laked washed red
cells.   Blood films showed :—

	Differential Leucocyte Count.					Nucleated red cells in 500 leucocytes.	Alterations in red cells.
	Lymphocytes.	Mononuclears.	Fine Oxyphiles.	Eosinophiles.	Basophiles.		
Day of inoculation	42·6	7·0	43·4	0·8	6·2	0	Normal.
1st day ...	24·0	2·0	68·6	0·6	4·2	1	Normal.
2nd day ...	18·6	2·2	77·6	0·2	1·4	2	Many blobs.
3rd day ...	32·8	5·0	61·2	0·0	1·0	55	All show blobs.

As before, blobs were not found in polychromasic red cells,
which occurred in megalocytic form in large numbers on the
third day, nor in normoblasts.   The marrow gave the following
results :—

Giant cells	1·2	
Small primitive cells	26·6	Total
Halo cells	5·6	lymphoids
Large primitive cells	9·6	= 70·6 per cent.
Small lymphocytes	5·2	
Large primitive lymphocytes	21·6	
Large mononuclear lymphoids	2·0	
Fine oxyphile	18·2	Total
Coarse oxyphile	2·0	leucoids
Basophile	2·6	= 28·2 per cent.
Polynuclear leucocytes	5·4	
Primitive erythroblasts	3·8	Total
Megaloblasts	9·4	nucleated
Normoblasts	11·6	red cells
Free nuclei	9·4	= 34·2 per cent.

This animal, therefore, also showed a very active lympho-
erythroblastic marrow.   The similarity with the preceding case
should be noted and contrasted with the great difference between
the hæmal leucocytes in the two cases.

Rabbit 5.—Male, 2050 grams ; 1 cc. aniline subcutaneously.
Four days later the blood was very slightly brown, and showed
no band in the red ; many of the red cells were large and pale.

Some microcytes are present, and a few cells show blobs. Of the white cells 64 per cent. were lymphocytes, 29 per cent. finely granular oxyphil polynuclears, and 90 nucleated red cells were found in counting 500 leucocytes. The marrow gave :—

Giant cells	0·6
Small primitive cells	24·0 ⎫
Halo cells	6·8 ⎪ Total
Large primitive cells	5·2 ⎬ lymphoids
Small lymphocytes	2·8 ⎪ = 49·8 per cent.
Large primitive lymphocytes	10·6 ⎪
Large mononuclear lymphoids	0·4 ⎭
Fine oxyphil	36·0 ⎫ Total
Coarse oxyphil	1·0 ⎪ leucoids
Basophil	1·0 ⎬ = 49·6 per cent.
Polynuclear leucocytes	11·6 ⎭
Primitive erythroblasts	3·4 ⎫ Total
Megaloblasts	9·0 ⎪ nucleated
Normoblasts	16·6 ⎬ red cells
Free nuclei	20·4 ⎭ = 49·4 per cent.

The erythroblastic apparatus is evidently very active; it shows, however, only the early stage, *i.e.*, an increase in the immediate rather than the remote precursors of the red cells, the lymphoids being normal.

SUMMARY.

1. Aniline is very poisonous to rabbits apart from its action on the blood.

2. Loss of oxygen-carrying power in the blood is, in our experience, a very rare cause of death.

3. Acute blood destruction by aniline may be associated with a very large increase in the volume of the blood.

4. Abnormal pigments are produced in the blood, (*a*) a brown pigment without any spectroscopic characters; (*b*) a pigment, probably brown, which shows a band in the red, but which is not methæmoglobin.

5. Histological changes in the red cells are :—

   (*a*) Destructive : " blobs," fragmentation.

   (*b*) Regenerative : polychromasia, nucleated red cells, etc.

6. The destructive changes in the blood, both pigmentary and histological, cannot be produced by aniline *in vitro*, and are probably not directly due to aniline itself.

7. The histology of the bone marrow of rabbits is described, and a developmental classification of the different varieties of leucoblastic and erythroblastic cells is given.

8. The changes in the marrow cells found after aniline poisoning are described.

KIDNEY TUMOURS.

By

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THE object of the present paper is not to give a detailed classification of all the tumours of the kidney, such as has appeared in the fifty-ninth volume of these Reports in an exhaustive monograph by Mr. Richards,[16] but rather to dwell on certain points in the structure and the ætiology of these growths which appear to be of special interest. Not only do the kidneys form the starting point of many big neoplasms, but an examination of post-mortem material discloses a surprisingly large number of small tumours in these organs, which are generally entered in the reports as "fibromata," if, indeed, they are deemed worthy of being mentioned at all. Insignificant though they may be, it is yet by their study that we gain a not inconsiderable amount of insight into the ætiology of the large new growths, since they help to clear up many extraordinary findings, such as muscle, both plain and striated, in the "sarcomata" of infants.

Without some knowledge of the development of a part, it is impossible to arrive at a full understanding of its diseases. I propose, therefore, first to give a short account of the most recent work on the embryology of the kidney. I shall next discuss arrests of development and embryonic tumours. Then I shall deal with the small renal tumours and with carcinomata, and finally describe adrenal rests and discuss the "hypernephromata" or "suprarenal-rest tumours." Detailed descriptions will be given of such cases as may be necessary. No

mention will be made of the sarcomata of adults, since there have occurred no cases of sufficient interest to deserve to be recorded.

Before proceeding further, I beg to thank the members of the Guy's Hospital staff for kindly allowing me to use their cases. A list of those authors only whose works have been quoted in the text is given at the end of this paper. For a very full bibliography the reader is referred to the fifty-ninth volume of these Reports.

DEVELOPMENT.

The kidney is developed in two parts. The ureter grows forwards from the posterior end of the Wolffian duct, which is, in part at least, derived from the epiblast. Its anterior extremity comes into close contact with a mass of mesoblastic tissue, known as the intermediate cell mass. It now breaks up into hollow branches, which end in blind dilatations or ampullæ. These ampullæ acquire a solid cap of mesoblastic cells, in which eventually a Bowman's capsule and a tubule are formed by the appearance of a lumen. These mesoblastic tubules join the ampullæ and grow in length, eventually forming the first and second convoluted tubules, the loops of Henlé, and the junctional tubules. It appears, then, that the only part of the epithelium of the kidney which is derived from the Wolffian duct is that of the pelves and the collecting tubules.

Bowman's capsules at first consist of a solid mass of cells projecting into a space, which is lined by a layer of cubical epithelium. Later capillaries develop within this solid mass. The cubical cells of the parietal layer of Bowman's capsule soon become flattened, and later those covering the tuft of capillaries. This latter event, however, does not take place until late, and the glomeruli of infants one or two months old can commonly be observed to be covered by a layer of distinctly cubical cells. Of the mesoblastic part of the kidney the Bowman's capsules are the first to become fully differentiated.

In the early embryo there is a large excess of connective tissue in the kidney, which gradually diminishes in amount, until in the adult it is reduced to a mere framework of fibrils which support the urinary tubules.

The fœtal ureter is surrounded by a thick connective-tissue envelope, which contains bundles of unstriped muscle, arranged in a concentric manner around the epithelium. This muscular layer accompanies even the collecting tubules. In the adult it is merely represented by some muscle bundles in the mucous membrane of the pelvis.

It is important to note that the capsule of the kidney also contains a fair amount of plain muscle, which may occasionally form thick bundles.

In the foregoing paragraphs the teaching of Bryce[3] and of Hertwig[10] has been followed. A very clear account of the development of the kidney has been written by Herring.[9]

DEVELOPMENTAL ERRORS, AND TUMOURS ARISING THEREFROM.

An arrest of development may take place in the kidney, which may occur over the whole of one or both organs, or may be limited to a few circumscribed areas. Either the two parts of the kidney may be formed naturally, but fail to unite, or the structures developed from the mesoblast may be imperfectly formed. In the former case the glomeruli and tubules will be fully developed, and secretion will take place; but, as the tubules end blindly, this will be retained, and produce the condition known as cystic kidney. In the latter case we expect to find either the whole or part of a kidney remaining in an undifferentiated embryonic condition. Such areas of arrested development almost invariably give rise, within the first few years of life, to a tumour formation, so that it is extremely rare to find them in an otherwise healthy kidney. This condition is, however, frequently observed in otherwise normal calves, in which animals it is said to disappear spontaneously. I have been able to find only one such case which occurred in the human subject. It was published by E. Meyer,[13] and was found in an

infant with many other congenital abnormalities. There now
follows a description of a similar case :—

Alice W., æt. 10 months, was admitted under Sir E. Cooper
Perry for broncho-pneumonia. At the autopsy purulent
bronchitis and broncho-pneumonia were found in both lungs.
The kidneys were of the size of those of an adult. Their
cortex was occupied by numerous white, roughly triangular
areas, the largest being a centimetre in diameter; they
projected slightly above the surface. Between them the
kidney was healthy, the distinction between cortex and
medulla being quite conspicuous. These nodules were
diagnosed as sarcoma, and the kidneys were, unfortunately,
not preserved. The other organs were healthy. Under the
microscope these areas present a richly cellular appearance.
There are numerous masses of small round cells, with large
deeply-staining nuclei and practically no cell bodies, which
closely resemble lymphocytes. Gradually these cells acquire
a definite cytoplasm around the nucleus, and so become
larger. The nuclei also enlarge somewhat. These big cells,
when fully formed, present two characteristic types, one of
which consists of large cells with an abundant cytoplasm,
which stains readily with eosin and resembles the epithelium
of the convoluted tubules ; the other, of smaller cells, whose
bodies stain of a bluer tint and which resemble the epithelium
of the straight tubules and loops of Henlé. Both these
forms arrange themselves into solid cylinders, which
gradually become more and more defined, and stand out
from the surrounding tissue. A lumen next appears by the
breaking down of the central cells, whose nuclei show all
stages of pyknosis and disintegration. Eventually both
convoluted and straight tubules are formed. The glomeruli
in these areas are in a much higher stage of development,
the youngest consisting of bunches of cubical and spheroidal
cells, which project into a space, the Bowman's capsule. At
their points of attachment these cells are continuous with,
and obviously spring from, the indefinite cells which surround
them. The capsules are lined by a layer of cubical or

flattened cells. The flattening takes place very early, so
that quite young Bowman's capsules may be almost entirely
lined by flat cells, whereas the epithelium covering the
glomeruli is still cubical in shape. Later, capillaries appear
in these glomeruli and form loops within them. The
connective tissue stroma consists of a few spindle cells and
endothelial cells lining the capillaries.

The junction between these areas and the surrounding
kidney substance, which is healthy, is gradual and without
signs of an inflammatory reaction. None of these areas
contain any traces of collecting tubules, which, of course,
are of independent origin, being outgrowths of the ureter of
the embryo.

Here we have an appearance closely resembling that of the
developing kidney. All stages, from the earliest indifferent cells
to the fully-formed glomeruli and tubules, can be made out. It
will be noticed that the Bowman's capsules are more highly
developed than the tubules, and that the epithelium lining their
parietal layers assumes the adult flattened shape much sooner
than does that covering the glomeruli. Another noticeable
feature is that the youngest capsules are occupied by solid
masses of cells, which at first contain no capillaries. This
appearance substantiates the view now held, that the glomeruli
are not formed by invaginations of capillary loops driving before
them the cells of the intermediate cell-mass. Of special interest
is the fact that the lumen of the tubules is formed by the breaking
down and disappearance of the central cells of the cylinders,
and is not due to a process of secretion. I have observed the
same appearance in the kidney of a three months' fœtus.

The entire absence of any inflammatory reaction at the peri-
phery of these nodules shows that they are not neoplasms, but
an essential part of the kidney, which acts in no respect like a
foreign body. It is interesting to speculate on what might have
happened if this child had continued to live. It is quite possible
that these areas might eventually have reached their full develop-
ment. Since, however, there were no collecting tubules present
within them, union of the mesoblastic and Wolffian elements

could not have taken place, and at best a localised form of cystic kidney would have resulted. This absence of collecting tubules in the areas of arrested development explains the occurrence of the latter. For some reason, insufficient branches were formed at the end of the developing ureter. Some areas of the kidney were, therefore, not supplied by them, and these areas, being unable to unite with their respective non-existent collecting tubules, remained in an undifferentiated embryonic condition.

It is possible that one or more of these areas, sooner or later, would have assumed a malignant growth and have given rise to a so-called "embryonic tumour" of the kidney.

Very little connective tissue was present in these nodules. This must be taken to refer to differentiated connective tissue. The small round cells resembling lymphocytes are obviously in such an early stage of development that they may, and probably do, still retain the power of developing either into connective tissue or into epithelium.

The large size of the kidneys must not be regarded as being due to an excessive laying down of the material from which these organs were built up, but simply as a compensatory hypertrophy of the functioning parts, such as takes place when a large area of renal substance has been removed or rendered functionless. Since, from developmental considerations, it is unlikely that glomeruli can ever be formed in post-fœtal life in a compensatory hypertrophy, it can only be the tubules which grow in length and are able to branch. In such a case the glomeruli ought to be relatively diminished in numbers. I am not prepared to say, from an examination of the sections, if this is so in the present case.

This specimen represents areas of the undifferentiated mesoblastic tissue of the kidney, which for some reason have been arrested in their development, and were, at the time of death, still in a state of active growth.

This case is of great interest when we come to consider the peculiar class of tumour which occurs in the kidneys of children, and is known under the names of "sarcoma of infants," "adeno-

sarcoma," "embryonic tumour," etc. An exhaustive paper on the subject has recently been written by Hedrén.[8]

Several such cases have occurred in Guy's Hospital. The oldest subject was a woman of forty, whose left kidney was entirely replaced by a large new growth measuring 10 by 5½ inches in diameter. The right kidney was occupied by a circular tumour measuring 6 inches in diameter, which was found to be an hypernephroma. These tumours are, however, usually found in young children, and have even been observed in the fœtus. They originate in the kidney substance, with which they are generally very loosely connected, so that they are easily shelled out from it. They are surrounded by a capsule composed of compressed and atrophied renal tissue. Two or more tumours may be present in the same kidney. Cut sections present fibrous trabeculæ, the spaces between which are filled with a soft brain-like tissue.

On microscopic examination different parts are found to vary considerably in structure. The coarser trabeculæ consist of fibrous tissue in which there often remain glomeruli and tubules, showing that some of them at least represent atrophied kidney substance. From these septa there arise delicate trabeculæ which separate the tumour into lobules. These trabeculæ are composed of spindle cells with long nuclei and a granular protoplasm, which stains readily with eosine. Some of the nuclei are very long and rod-shaped, and obviously belong to plain muscle-fibres. Only once have I been unable to find any evidence of unstriped muscle in the sections examined (Museum No. 1655 *).

The lobules between these septa consist of collections of small round cells with large, deeply-staining nuclei and very little cytoplasm. These cells grow in size, and arrange themselves into solid columns, which are converted into tubules by the appearance of a central lumen. A characteristic feature of these tumours is the way in which these tubules grow out from the surrounding mass of cells. At first they appear to be merely

* The numbers refer to the third edition of the Guy's Hospital Museum Catalogue, London, 1899.

condensed areas of cells, which shade off into the surrounding tissue.   Later they stand out more clearly; the cells composing them become cubical or columnar, and rest on a well-marked basement membrane.   These tubules show a marked tendency to branch.

Other areas consist of well-developed tubules, with but a few masses of undifferentiated small round cells.   They are surrounded by myxomatous connective tissue, composed of spindle, branching, and stellate cells, and are parts of the growth which have reached a higher stage of development.

I have observed collections of round cells lying within a space, and closely resembling glomeruli in an early stage of development.   In the specimens preserved at Guy's Hospital these appearances are, however, rare, and have to be carefully searched for.

Some cases occur in which the tubular formations are very scanty.   These specimens, at first sight, would be called pure round-celled sarcomata.   Tubules can, however, in every case be found if sufficient sections be carefully examined.

Metastases most frequently occur in the lungs and the liver. Histologically they resemble the primary growth.   Before discussing the ætiology of these tumours, it will be necessary to give a short account of the one already mentioned, which occurred in the left kidney of a woman of forty:—

> The connective tissue contains many unstriped muscle-cells.   Masses of undifferentiated small round cells occupy the meshes of the trabeculæ.   At their periphery these cells grow in size by the accumulation of cytoplasm around their nuclei.   Connective tissue appears between them, and they arrange themselves in the form of solid cylinders which acquire a lumen.   Irregular greatly convoluted tubules are thus formed, which grow for a long distance into the thick connective tissue septa which divide the lobules.

> When there is a large blood-vessel these cylinders and tubules radiate outwards from it in a remarkable manner. This is due to the fact that the connective tissue septa are arranged radially, like the spokes of a wheel.   When

the epithelial cylinders are solid, an appearance closely resembling the suprarenal is produced. This resemblance becomes most marked under the capsule of the tumour. Here the alveoli are much compressed, and many of the epithelial cells have become vacuolated and partially disintegrated from pressure. The resemblance to suprarenal tissue here is very striking, and is rendered all the more so by the fact that the connective tissue is practically limited to a network of capillaries, which lie between the acini of epithelium. If this tissue is traced into the deeper parts of the growth, when the pressure and consequent degeneration are less marked, the gradual change from this suprarenal-like structure to that of the bulk of the new growth can be easily made out. This appearance is of great importance, and will be referred to again under the heading of the hypernephromata.

Various views as to the origin of these tumours have been entertained. By some, who neglected the tubules, they were regarded as sarcomata, by others as remains of the Wolffian body. When we remember the characteristic appearances of tubules growing out from the masses of undifferentiated cells, the resemblance of these growths to the developing kidney becomes obvious. In the youngest parts we have numerous small round cells, from which rudimentary glomeruli and tubules are being formed, an appearance closely resembling the growing subcapsular portion of the developing kidney. In the more advanced areas we get well-developed tubules surrounded by myxomatous " embryonic " connective tissue, such as is seen in the deeper parts of a kidney of, for instance, a six months' fœtus. It is, therefore, quite unnecessary to call to our aid remains of the Wolffian body. These tumours should be regarded as being developed from the kidney itself. Wolffian remains have, to the best of my knowledge, never as yet been found in the kidney. These neoplasms are sometimes multiple, and may show slight differences, such as a higher development of the tubules, a greater amount of plain muscle, etc. If we regard them as being derived from remains of the Wolffian body, we must assume the presence of several

such remains in different stages of preservation. It seems far more reasonable to conclude that such tumours have originated in areas of undifferentiated kidney substance, which are known to occur. All their histological characters can be accounted for on such an hypothesis. The cause, whatever it may be, which, at an early period of development, produces the arrest of one area of the kidney is likely to persist, and to cause the arrest of other areas at the same or a subsequent period. In support of this view Hedrén mentions that he has occasionally found around the new growth a zone of undifferentiated renal tissue which had not participated in the tumour formation. In such a case the growth merges gradually into the kidney substance, and cannot be easily shelled out from it.

With regard to the presence of plain muscle, it must be remembered that the kidney during fœtal life is very rich in this tissue. In the adult it persists both in the capsule and in the wall of the pelvis. Since the whole of the kidney, with the exception of the pelvis and collecting tubules, is mesoblastic in origin, this muscle must come from the same cells, which also form the renal epithelium. Areas in which development has been arrested at an early period will contain the mother-cells of the epithelium and of the plain muscle.

Occasionally other structures, such as striated muscle, cartilage, bone (Hedrén), stratified and ciliated epithelium are observed in the embryonic tumours of infants. One such case has occurred in Guy's Hospital (Museum No. 1660). Here stratified epithelium, striated muscle, and cartilage are to be found :—

> This tumour was removed by Mr. Jacobson from a girl of 14, who died four months later from recurrences. The kidney is replaced by a soft, spongy new growth, except above where there is some renal substance still preserved. The pelvis is invaded by a large mass of the growth. Towards its upper pole this tumour presents, at its outer surface, a harder, well-defined area, which on section shows a fibrous appearance.

> Under the microscope this case is an embryonic tumour. The greater part of the sections is composed of masses of

round cells, which group themselves into cylinders and tubules in the characteristic manner. The most highly-developed tubules possess a cylindrical epithelium and a definite basement membrane. Among the masses of undifferentiated cells there occur numerous collections of squamous epithelium, the cells of which have undergone a horny change and stain a blue colour by Gram's method. Some of these squamous areas are well defined and stand out from the surrounding tissues. Others are intimately blended with the surrounding small round cells or rudimentary cylinders and tubules, so that it is often difficult to be certain when these cells change into the squamous type. It is obvious, however, that we are dealing with a conversion of the embryonic cells into squamous epithelium, and that the latter is not of independent origin. The connective tissue septa are composed mainly of unstriped muscle, whose cells penetrate between the epithelial masses. Numerous striated cells occur among them. These may be round and contain an oval nucleus; or long, with several nuclei which occur in small groups of two or three and occupy a central position, producing a localised bulging of the cytoplasm. Striation is usually obscure, but all these cells stain very deeply with eosin. This striped muscle is most abundant and highly developed in the hard area of the tumour, but its cells occur even in the centres of the epithelial masses. Transitional stages between the striated and plain muscle have not been observed to occur. The cartilage is of the hyaline type and occurs as isolated nodules, surrounded by a definite perichondrium, or as quite unencapsuled groups of cells which blend with the surrounding connective tissue, and between which a hyaline matrix appears.

In this case we are dealing with an embryonic tumour of the kidney, in which, in addition to the usual tissues, there are present squamous epithelium, striated muscle, and cartilage. From an examination of the sections it is, I think, obvious that this is a neoplasm which has started in kidney tissue, and not an embryoma, which has become associated with an embryonic

renal tumour. Such an embryoma would represent an included twin or a cell which had become separated off at an early stage of embryonic life, before the primary germinal layers had become established, and had, after a period of quiescence, assumed active malignant growth. Such a cell would be able to form epi-, meso-, and hypoblastic tissues, and we could thus explain the presence of squamous epithelium, etc., in this tumour. We should then, however, expect to find that the growth of the squamous epithelium was independent, and not intimately associated with the rudimentary kidney tubules, as is actually the case in the specimen under discussion ; for it seems very unlikely that the greater part of such an embryoma would possess the structure of a renal tumour, which is the same as saying that its greater part was composed of kidney tissue. I believe this tumour is analogous to cases of squamous epithelioma occasionally found in the intestine, gall-bladder, pancreas, etc., and that the presence in it of horny cells must be explained as a case of metaplasia, *i.e.*, the assumption by the cells derived from one germinal layer (*i.e.*, the mesoblast) of morphological characters belonging to the cells of another layer (the epiblast). Embryologists have laid far too much stress on the immutability of the germinal layers--that a cell destined to form a part of, for instance, the small intestine, can never come to resemble a cell of the epithelium covering the surface of the body. The truth seems rather to be that the differentiation of the germinal layers is a functional one—that a cell going to form part of the epithelium of the small intestine becomes columnar solely for the reason that this is the most useful shape that it can assume, --but that, if this cell should for some reason be displaced outward on to the surface of the embryo, it will develop into a tough horny cell. Therefore, in certain pathological conditions, the cells of one layer are able to assume the characters of those of another layer, from causes that we do not as yet understand properly, but which may be allied to long-continued irritation. These causes seem occasionally to be in force in tumours such as the present one, and they ought to give us pause and to show us that we cannot expect to arrive at the truth by the study of

merely one class of phenomena, such as those of embryology, but that even pathological conditions may occasionally throw an important light on the problems of development.

Since a tumour which, in its greater part, possesses the structure of an embryonic kidney tumour, has been shown to contain squamous epithelium, one might be tempted to argue that this class of new growth does not really originate in the kidney, but is some kind of embryoma. The close similarity to the developing kidney, however, precludes this view from being accepted, since all stages, from undifferentiated round cells to well-developed renal tubules, can be made out.

CYSTIC KIDNEYS.

Practically everything that has been said of the ætiology of the embryonic tumours may be repeated of cystic kidneys. The former represent areas of arrested development which have undergone a tumour formation, the latter are similar areas which have undergone the greatest degree of physiological differentiation possible under the circumstances.

Cystic kidneys are often congenital, and are found with decreasing frequency as life advances. The condition is not infrequently bilateral, and may vary from a mass of cysts, which are separated only by thin bands of functioning kidney substance, to a few cysts in an otherwise healthy organ. The latter form is seen not uncommonly at post-mortems. The surface of the kidneys is smooth, and scattered over it there are a varying number of cysts, from one or two to several dozens. These cysts usually occupy the cortex, but are sometimes present in the pyramids as well. A very good example occurred last year in a child two years old (1908, No. 248). Only one kidney was affected ; it contained several collections of small cortical cysts. I have examined sections of several such cases, and have been unable to find any evidences of chronic interstitial nephritis, such as would cause blocking of tubules with subsequent dilatation by the accumulation of secretion.

The cysts often contain the remains of a glomerulus. Others are surrounded by bands of plain muscle. The epithelium is

flattened, cubical, or columnar. Diverticula grow out from the tubules. These may branch and extend for some distance into the connective tissue.

All these cysts end blindly. The condition is due to a failure of union of the mesoblastic and Wolffian elements of the kidney. Development and function, however, go on, producing dilatation of the blind tubules with the formation of cysts.

Small Tumours of the Pyramids.

The conditions hitherto described can all be shown to be due to an arrest of development of the kidney. These undifferentiated areas may persist more or less unaltered, may attain full development and differentiation, but fail to unite with their appropriate Wolffian tubules, or, lastly, may give rise to true neoplasms with metastases.

There is, however, yet another tumour of the kidney, which can be explained on the same lines. On systematically examining the kidneys at post-mortems, in about 5 to 8 per cent. rounded or oval white nodules are found in the pyramids. They are well-defined, fairly hard, and stand out above the neighbouring tissue. In size they vary from a speck just recognisable with the naked eye to nearly a centimetre in diameter. Two such nodules may occur in the same pyramid. The largest number I have counted in one kidney was seven. They occur at any age, but, owing to their generally minute size in infants, and to the fact that they grow with the kidney, they are usually only obvious in adults. It is often necessary to cut up the whole kidney into thin strips, 4 to 5 mm. in thickness, in order to make certain of not missing them. Busse[4] describes an analogous case in a boy one year old, who had deformed hands. He has often found these tumours to contain plain muscle and epithelial tubules. Nürnberg[14] was unable to find muscle in them, and thinks that some are tumours arising in an area of maldevelopment, whereas others are due to atrophic changes and sclerosis of the connective tissue. Some of the nodules I have examined are undoubtedly due to the latter cause. They occur in kidneys which are undergoing a granular

change, and are merely localized patches of sclerosis, and not neoplasms.

The majority are, however, neoplasms. They can usually be shown to consist of two areas: a central one, in which the connective tissue is arranged in whorls, such as are seen in fibromata, and a peripheral zone, composed of sclerotic kidney substance. The central area contains a few tubules lined by a columnar epithelium and possessing a definite basement membrane, around which there is usually a ring of condensed fibrous tissue. Extensive necrotic changes can often be observed, most marked in these rings around the tubules. There are other epithelial elements to be seen, namely, columns and tubules, which extend from periphery to centre in a radial manner. Their nuclei are large and stain deeply, and their cytoplasm is scanty. I believe that they are newly-formed tubules, which grow into these areas from the surrounding tissue.

The peripheral zone consists of sclerotic fibrous tissue, and contains the remains of atrophied renal tubules, which have been pushed aside by the tumour. The central area is occasionally made up of myxomatous tissue with long spindle-shaped and branching cells. In such a case the periphery does not show this structure, but consists of ordinary fibrous tissue.

Only once have I been able to find plain muscle in one of these nodules. It was represented by thin bands and isolated cells, with definitely rod-shaped elongated nuclei and a granular protoplasm.

It is, I think, certain that we are here dealing with a tumour formation. The arrangement of the fibrous tissue, the sharp contour of these nodules, and the way in which the surrounding renal tubules are pushed aside, all substantiate this view. I have been able to confirm Busse's finding of plain muscle, and agree with his view that the tumour has arisen in fœtal remains. It will be remembered that, during early embryonic life, the collecting tubules, derived from the Wolffian duct, are surrounded by unstriped muscle, which disappears as development proceeds. This disappearance may, in some cases, be incomplete, so that small rudiments of muscle may occasionally remain in the

pyramids, which at a late period acquire active independent growth and give rise to small myomata. As life proceeds, the connective tissue surrounding the muscle grows at the expense of the latter, so that by the time the tumour has reached any size it has entirely replaced it. An indication of such a replacement is afforded by the rings of condensed connective tissue around the epithelial tubules, which are the remains of the collecting tubule whose development has been arrested. The occasional myxomatous condition of the central areas may be due to œdema. If this were so, we should expect the sclerotic peripheral zone occasionally to participate in this change. It may, I think, with fairness, be explained as an embryonic condition, the tumour possessing the form of embryonic connective tissue, such as is seen in the kidney of the six months' fœtus.

The greatest argument against these nodules being embryonic tumours is their absence, or great rarity, in infants. Here, however, they may be so small and undeveloped that they are invisible to the naked eye, and only found with the microscope by the merest chance. It would be necessary to cut serial sections of many infants' kidneys to arrive at a definite knowledge of their presence or absence.

CORTICAL FIBRO-MYOMATA.

It will be well to consider the cortical fibro-myomata in this place. They are small, white, roughly triangular nodules, which project above the surface of the kidney, and are always torn on stripping the capsule. This is owing to the fact that they are attached to the latter, and indeed originate within it. They are the hardest kind of tumour that occurs in this situation, and this character, together with their torn surface, is their best macroscopic distinguishing feature. They are often multiple. Microscopically, they contain bundles of plain muscle, arranged in an interlacing manner; these bundles are separated from each other by a varying amount of fibrous tissue. The tumours are quite unencapsuled, and may extend into the surrounding kidney for a considerable distance. In their deeper parts they often

contain the remains of glomeruli and renal tubules. There are never such remains on or under their free surface, an indication that they are derived from the capsule. The capsule extends over them, and they become blended with its substance. The largest fibro-myoma I have seen was ½ cm. in diameter. Busse[5] describes two large ones, one of which contained striped muscle.

It has already been stated that the kidney capsule contains muscular tissue, which may occur as thick bands. These tumours are to be regarded as fibro-myomata arising in connection with this muscle.

Occasionally these nodules are composed of spindle and round cells, when they closely resemble a sarcoma. I have seen a case which consisted partly of this tissue and partly of adult plain muscle. Such tumours may occasionally form the starting-point of large sarcomata. Bland Sutton[2] says that sarcoma of the kidney in adults arises under the capsule. Lipomata are common in and under the capsule. In the latter case they may extend into the kidney substance.

<div align="center">ADENOMATA.</div>

The next class of tumour to be considered is the so-called adenoma of granular kidneys. These tumours are exceedingly common, but, owing to their minute size, are often overlooked and only found accidentally in microscopic sections. Adenomata, large enough to be seen with the naked eye, occur in about 5 per cent. of all granular kidneys. They are rounded nodules, which may occur in any part of the cortex. Usually, however, they are placed superficially, and then project slightly above the surface of the kidney. They are of a white or yellowish colour, and may be 1 cm. or more in diameter. At times they are definitely unencapsuled, at others they shade off gradually into the surrounding renal substance. They may develop in a scar on the surface. I have seen three such tumours, lying side by side, in such a scar. Occasionally the whole of a kidney may be studded with these nodules. Such a case occurred at post-mortems some time ago. The affected kidney was small and granular. Its surface and cortex were studded with numerous

white nodules, varying in size from 1 cm. downwards, which were all adenomata.

When an adenoma develops in one of those depressed granular areas, so common in chronic nephritis, it lies below the surface ; otherwise it always projects above it.

Under the microscope the commonest form of adenoma is seen to consist of a cyst-like space, usually surrounded by a wall of coarse fibrous tissue, which shades off gradually into the neighbouring kidney substance. The space is lined by a single layer of cubical or columnar epithelium, which is often flattened from pressure, and, in the larger tumours, may entirely disappear. From the wall trabeculæ project into the lumen of the space, which are composed of a small amount of delicate connective tissue, and contain a central thin-walled blood vessel. These trabeculæ branch in an irregular manner, but, if outline drawings of serial sections going through the whole of a tumour be made, it will be seen that these septa are not true papillæ with a blind ending, but always join the cyst wall again ; so that, however much this growth may resemble a papilloma, it really consists of dilated, very irregular tubules. This only applies to the primary septa, from which short true papillæ are often given off, which may branch a little, but usually end very soon. The trabeculæ are covered by a single layer of epithelium which, when well developed, consists of very tall columnar cells with round darkly staining nuclei, and a cytoplasm which stains intensely with eosin. The nuclei show a tendency to lie near the free and not the attached extremity of the cells. The cytoplasm is often granular and extensively vacuolated. Degeneration into a shreddy, colloid mass and hæmorrhages are frequent. Solid papillæ, composed only of epithelium, are often observed. Tubular processes grow down into the fibrous capsule and into the thicker trabeculæ.

When small, these tumours may be quite unencapsuled. They then resemble dilated renal tubules from which short papillæ project. This epithelium is taller and stains more deeply than does that of the surrounding kidney tubules, and the connective tissue in the septa is always present, and is an important

distinguishing feature. The surrounding renal tubules are slightly compressed. Only once have I been able to show a communication between the lumen of an adenoma and a kidney tubule, in a case presently to be described.

Another class of adenoma possesses an obviously tubular structure. There are trabeculæ composed of a delicate young connective tissue, covered by a layer of cubical epithelium, which is far shorter and stains much bluer than that of the forms just described. These growths are unencapsuled, and extend between the tubules of the kidney, from which they can easily be distinguished by their darker staining.

Nùrnberg was unable to show their connection with the surrounding renal tubules. I have been able to demonstrate this connection once only, in the case of an entirely unencapsuled tumour of this kind. Here, in several sections of a series, the dark tumour cells are seen side by side in the same tubules with the lightly staining renal epithelium. As far as I am aware, this is the first time that such an appearance has been observed. Usually, even when there is no connective tissue around the tumour, its tubules can, in serial sections, be shown to end blindly between those of the kidney. Where a capsule is present, this appearance becomes more marked, and the tubules of the new growth can be traced for some distance into the surrounding tissues. On the whole, these tumours show but few signs of active growth. Retrogressive changes can often be seen in them, and they seem to have a low vitality, and probably often disappear spontaneously.

We have, then, a form resembling a papilloma, but really composed of highly convoluted and intercommunicating tubules, in which the epithelium assumes a tall columnar shape, and in its staining powers closely resembles that of the convoluted tubules of the kidney. We also have a tubular form with cubical epithelium which presents no marked characters, being composed of small cubical cells; this form has been shown to communicate with a renal tubule. A still earlier form can occasionally be seen. This consists of a dilated kidney tubule, whose epithelium has become very tall. This tubule is highly convoluted, and the bends

between the convolutions resemble papillæ. The epithelium also tends to grow into the lumen in solid clumps. Such dilated tubules are occasionally found in the fibrous areas of granular kidneys, and may communicate with a convoluted tubule, whose epithelium may be extensively degenerated. I believe this appearance to be the first step towards the production of an adenoma. It is obviously a condition of hyperplasia, possibly with the object of making up for lost epithelium, but can hardly be considered to be a neoplasm. Later this hyperplasia increases, the tubule affected becomes more and more convoluted, though still communicating with the tubules above and below it, its cells assume an independent growth, and form processes which grow out into the surrounding tissue. The borderland between hyperplasia and true tumour formation is thus reached. If the growth of the cells goes on, the surrounding tissue becomes compressed and destroyed, and the tubules grow out in an independent manner; an adenoma is thus produced. That this independent growth may proceed until it assumes a malignant type with the production of metastases is shown by the way in which the epithelium occasionally grows deep down between the neighbouring renal tubules, or far into the capsule; also by the structure of many carcinomata of the kidney. This malignant growth is, however, not often reached. From a consideration of the appearance of these adenomata, which only rarely show signs of rapid growth, and which usually contain evidence of degenerative changes, it appears very probable that the majority of them disappear again. Occasionally one sees cysts in granular kidneys which contain traces of septa, and are filled with epithelial débris. These are, I think, the remains of degenerated adenomata.

It is important to note that this form of new growth is practically never seen except in granular kidneys, and becomes progressively commoner with advancing age. A few cases have been recorded in otherwise healthy kidneys; *e.g.*, by Manasse.[12] This almost constant association with granular changes in the kidney is a strong point in favour of these tumours being caused by hyperplastic changes in the renal tubules, with the object of

compensating for lost epithelium. Such regeneration can be observed occasionally in granular kidneys, and occurs both in the convoluted and straight tubules. A twisted mass of epithelium, whose nuclei stain deeply, and whose cell-bodies are small, is seen occupying a space which is the remains of a straight tubule. Stœrck,[17] has recently investigated these changes very fully, and has shown that regeneration of epithelium in chronic nephritis is of frequent occurrence.

Glomerular Tumours.

The tumours so far considered have all originated in the epithelium of the secreting tubules of the kidney. There are, however, a few cases on record in which their starting-point has been the glomeruli. Abram,[1] Hildebrand,[11] and Sharkey,[16] have published such cases. In Abram's case the parietal layer of Bowman's capsules was lined by several layers of columnar epithelium, which infiltrated the surrounding connective tissue. The epithelium over the vascular tufts was normal. There were metastases on the ribs, sternum, vertebræ, pleuræ, lungs and liver. The case of Sharkey is very similar, but may possibly be a squamous epithelioma arising in an ovarian dermoid, with an independent new growth of the glomeruli. Abram's case appears to be a primary carcinoma of the glomeruli.

The following is a description of a kidney tumour, which may have started in a glomerulus :—

Insp. 1902, 508. Museum 02⁵⁴.—William S., æt. 6ᴅ. Fibroid, hypertrophied, and dilated heart, atheroma of aorta and pulmonary vessels. Lungs emphysematous, congested and œdematous. Kidneys.—Weight 421 grm. Normal in appearance. Projecting from the external border of the left kidney, exactly half-way between the two poles, there is an oval yellowish tumour 3·8 by 2·5 cm. in diameter. It is separated from the kidney by a deep sulcus, and presents a slightly irregular surface. The cut surface of the tumour consists of several lobules, separated from each other by connective tissue septa. It extends for about 1·5 cm. into the substance of the kidney, and is limited

below by a pyramid. It is surrounded by a fibrous capsule. The whole of this tumour, therefore, lies within the cortex; ½ c.m. below it there is a large multilocular cortical cyst. No other tumour was found at the autopsy.

Microscopic appearance :—

a. Of the kidney.—The blood-vessels are thickened. Under the capsule there are several patches of interstitial sclerosis, the fibrous tissue being old, and containing but few nuclei. The glomeruli are, on the whole, healthy. The vascular tufts are large, and the capillary loops well marked. Bowman's capsules often show a varying amount of thickening and increase of fibrous tissue, which may have proceeded to complete fibrosis and occlusion of the glomerulus. There is quite a large number of such fibrous glomeruli. A very noticeable feature in them is that a hyaline degeneration has occurred in these fibrous glomeruli, but nowhere else.

b. Of the tumour.—The capsule consists of atrophied and fibrosed kidney substance, from which large connective tissue septa project into the interior of the tumour, many of which contain thin-walled blood-vessels. From these septa there radiates in all directions a very irregular network of trabeculæ, most of which are coarse. Some are, however, very fine. All these trabeculæ are occupied by capillaries of varying sizes, so that the connective tissue is generally reduced merely to a ring around them. The most striking feature is that the whole of the connective tissue within the tumour has undergone a hyaline degeneration. This is very well shown in sections stained with v. Gieson. The walls of the capillaries within the trabeculæ are lined by a layer of flattened or slightly cubical endothelial cells. The spaces between the trabeculæ are, however, lined by large cubical endothelial cells, which have often proliferated so as completely to fill up the spaces, or have invaded the surrounding connective tissue, thus producing large nodules. Typically the inter-trabecular spaces do not contain blood, but there are several large areas of necrosis and of hæmorrhage where the structure of this tumour is very much obscured. The

resemblance of certain areas to the vascular tuft of a glomerulus is striking.

Here we are dealing with an angeioma or angeio-endothelioma, and not with an adenoma. I have, however, described this specimen here, since I believe it to be a tumour which has started in a glomerulus. It may, in a sense, be called an adenoma of a glomerulus. The irregular spaces, lined by cubical endothelial cells and containing no blood resemble the cavity of Bowman's capsule, whereas the trabeculæ with their numerous dilated capillaries resemble the glomerular tuft. In support of this view it may be noted that, whereas the whole of the connective tissue of the tumour had undergone hyaline degeneration, the only parts of the kidney to do so were the glomeruli.*

Carcinoma.

There are two possible sites of origin of carcinoma of the kidney: the secreting tissue, and the pelvis and calyces. Indeed, both these parts form the site of origin of malignant new growths, which can be distinguished from each other both by the naked eye and with the microscope. It will be well to study these two classes separately.

The tumours originating in the kidney substance present two forms, the diffuse and the nodular. The diffuse variety invades the kidney in all directions and eventually replaces its entire substance. It usually starts in the depths of the organ, since, with the microscope, the remains of renal tissue can often be made out at the periphery. This form may be soft and brainlike in consistency, or hard and fibrous. I believe, however, that some, at least, of such tumours arise in the pelvis; these specimens will be described later.

The nodular form always originates on the surface of the kidney. It is usually separated from the renal tissue by a

* Since writing this, Dr. Kettle, of the Cancer Hospital, has shown me a very similar tumour, which was removed at operation. The main distinction is that in this case extensive hæmorrhage had taken place, and the large endothelial cells were stained brown with the altered blood which they had taken up.

definite capsule (cf. Mr. Targett[19]), but may nevertheless reach as far as the pelvis, which it may even invade and break through, and grow for some distance along the ureter. As this form of tumour possesses a structure somewhat resembling that of the supra-renal, I will leave its microscopical description until discussing the hypernephromata.

Although the diffuse form originates in the depths of the kidney, the pelvis seems to offer a great resistance to being invaded by it. As the kidney becomes affected its tubules are occluded, and no urine can escape from these damaged tubules. This explains the rarity of hæmaturia in this condition. A great part of one kidney may be destroyed by carcinoma, and yet the urine be healthy.

As regards the microscopic appearance of renal carcinoma, it is composed of cubical and spheroidal cells, which tend to grow in large masses, with no very characteristic features. Occasionally, however, appearances can be observed which show that some of these tumours, at least, have originated in an adenoma. In the museum there is preserved a very good specimen in point :—

> No. 1645. A right kidney, removed from a woman æt. 26, which is extensively infiltrated by new growth, presenting a somewhat nodular appearance. The growth had invaded the renal vein and caused pulmonary embolism. Metastases in lungs, liver, and lumbar lymph-glands. Microscopically this tumour is a spheroidal-celled carcinoma. It extends into the kidney substance in the form of nodules, which are usually partially surrounded by a fibrous wall, from which there project in several places delicate connective tissue trabeculæ, containing a central capillary and lined by a tall columnar epithelium. These trabeculæ join each other, and enclose between them small spaces, into which more delicate secondary trabeculæ project. These parts of the tumour are identical with what has been described above in connection with adenomata.

There can, therefore, be no doubt that adenomata of the kidney may sometimes assume a malignant growth and give rise to metastases.

Other carcinomata possess a tubular structure. They contain small alveoli lined by cubical and columnar cells, and bounded by a small amount of connective tissue, which is often merely represented by the endothelial walls of capillaries. If the epithelial cells possess a homogeneous deeply-staining cytoplasm, these tumours are usually called columnar-celled carcinomata; if, however, the cells are extensively vacuolated, they are classed among the hypernephromata, a point which will be referred to fully later.

Renal tumours show a marked tendency to break through into the circulation. Not only is the renal vein often occluded by a malignant thrombus, as in a case recorded by Fagge,[*] but emboli of new growth may be discovered in the blood-vessels of the lungs.

Insp. 1909–35.—A lobulated tumour at the lower pole of the right kidney, metastases in the liver and lungs. Projecting from the wall of a large pulmonary vessel, and firmly adherent to it, there was an embolus, $\frac{1}{2}$ cm. in diameter, consisting of new growth, which is invading the intima of the vessel and becoming vascularised from it. Many of the small pulmonary metastases occupy the lumina of blood-vessels.

Carcinoma of the Renal Pelvis.

The tumours starting in the pelvis are usually associated with conditions of chronic irritation, such as stones. They may occur as papillary tufts projecting from the dilated calyces and pelvis, or uniformly infiltrate and enlarge the kidney, so that this organ is converted into a large solid mass of new growth in which branching calculi may be embedded. Occasionally such a tumour may closely resemble the nodular variety of carcinoma which starts in the kidney proper. Such a case occurred last year:—

Insp. 1908, 214.—The kidney is enlarged to twice its normal size. The middle three-quarters are occupied by a partially encapsuled, rounded, slightly lobulated tumour with many yellow areas of necrosis and of hæmorrhage. This tumour has extensively implicated the pelvis, and projects into it in the form of necrotic granulations. Above

this area the pelvis is free from new growth, but it is dilated and thickened. Two renal papillæ project into this part. The kidney substance is reduced to a strip above and below the tumour; the latter of these contains two, apparently isolated, nodules of growth. Metastases in lungs and liver.

The foregoing description would apply very well to a nodular carcinoma of the kidney or hypernephroma. The microscopic appearance was obscured by the large amount of necrosis and vacuolation of the cells. It was not until two similar tumours which are preserved in the Museum were examined that a correct diagnosis as to its nature could be arrived at. I will first describe these specimens and then their histology.

Museum, 1648. "A kidney, enlarged so as to measure seven inches in length, and uniformly infiltrated by a soft new growth which projects into the dilated pelvis of the organ and blocks the renal vein. The upper end of the ureter is distended for a distance of about 2 inches by a mass of growth continuous with that in the pelvis."

This description might again apply to a hypernephroma, from which it is impossible to distinguish this specimen. The following tumour, however, which presents the same microscopic appearance, conclusively proves the site of origin.

Museum, 1654. "A right kidney, at the inner margin of which is situated an oval tumour measuring three and a-half inches in its longest diameter. It is closely applied to the hilum of the kidney, but is not connected with this organ, which has been laterally compressed, and moulded to the convexity of the tumour. Anteriorly the growth is nodular, some of the nodules projecting into the dilated renal vein. On the back the surface is rough, and was firmly adherent. The cut section shows the growth to be composed of homogeneous material, traversed by coarse strands of translucent fibrous tissue."

Here, then, is a tumour which has started in the pelvis at some little distance from the kidney, which organ it had not invaded. A metastasis was found in an aortic lymphatic gland. I may add that there is nothing in the naked-eye or microscopic

appearance of this tumour to suggest that it might have originated in a displaced piece of renal tissue.

The microscopic appearance of these three specimens is very similar. The growth consists of a framework of connective tissue, which is arranged in the form of delicate trabeculæ and papillæ, many of which contain a central capillary. This is covered by very large columnar and cubical epithelial cells with big, round vesicular nuclei. In parts their cytoplasm stains deeply, but generally the staining is faint, and the cells may even be vacuolated. These cells proliferate very rapidly, so that the intervening spaces become filled by large masses of large irregular cells, which may assume a columnar, cubical, or even fusiform shape, so that parts of the sections resemble at first sight a very large spindle-celled sarcoma. Many multi-nucleated giant cells are present, which attain their maximum size in the pulmonary metastases of the first case, where they resemble large syncytia. In these metastases I have observed appearances strongly suggestive of commencing keratinization, but have been unable to stain them satisfactorily by Gram's method, possibly owing to the fact that the tissues had been fixed in formalin. Hyaline degeneration was well marked in the walls of the arteries of cases 1 and 3.

The large size of these cells and their clear vesicular nuclei resemble transitional epithelium somewhat closely. Since, in the first case, the alveoli are usually small and filled with cells which are so extensively degenerated that it was almost impossible to find more than an isolated healthy cell, and the connective tissue happens to be somewhat cellular, we at first called this tumour a hypernephroma. This opinion was strengthened by the examination of the naked-eye specimen. It was not until this case was compared with the other two that its true nature was arrived at.

Carcinoma of the renal pelvis may sometimes be a typical squamous-celled epithelioma with prickle-cells, keratinization, and horny cell nests. Museum specimen 99⁵² is such a case. Here the dead horny cells are extensively calcified. Such epitheliomata or cancroids, as they have been called, occasionally

appear in mucous membranes lined by other than squamous epithelium. It is not difficult to explain their presence in the renal pelvis, since this organ is formed from an outgrowth of the Wolffian duct, which is now considered to be derived, in part at least, from the epiblast. This layer almost always gives rise to squamous epitheliomata, and it is therefore not surprising if the epithelium of the renal pelvis, its descendant, occasionally does so likewise.

Suprarenal Tissue in the Kidney.

Suprarenal tissue is often found in the kidney. One or both suprarenals may be displaced and lie within or under the kidney capsule. They will then not be found in their normal position.

More frequently, however, these organs occupy their normal site, but in addition to them accessory suprarenal tissue is found in or under the kidney capsule. These accessory adrenals are usually very small, yellow, flattened areas, which lie on the surface of the kidney and project but slightly, if at all, above it. Occasionally they may attain a considerable size, as in Insp. 1908—609, in which a piece of suprarenal, 1½ cm. in length, was applied to the 'upper pole of each kidney. In the case of the left organ it sent a long tongue-like projection deep down into the renal cortex. Both suprarenals were present in their normal position.

Accessory suprarenals are frequently observed in other places. Mr. Targett[19] has seen them in the broad ligament of the fœtal uterus. I have found them on the under-surface of the liver and in the spermatic cord.

Under the microscope these nodules nearly always consist of suprarenal cortex, the cells of which are arranged in the manner characteristic of this organ, and may possess a healthy uniformly staining, or a highly vacuolated cytoplasm. They are usually only partially encapsuled, so that the suprarenal tissue often extends for some distance between the kidney tubules. Large specimens may contain medulla as well, as in Insp. 1908—609, in which the tongue-like process was totally unencapsuled, and to

contain within it pieces of renal substance, which it had enclosed during its growth.

A very noticeable feature of these accessory suprarenals is their benign appearance. There are usually no signs of active proliferation, and their epithelium seems to grow slowly between the renal tubules, which eventually atrophy. There are no signs of malignant growth and of destruction of kidney substance.

HYPERNEPHROMA.

Ever since Gravitz's[7] classical paper in 1883, in which he propounded the theory that hypernephromata of the kidney arise in aberrant suprarenal tissue, this explanation has been accepted by all pathologists. Sudeck[18] was, for a long time, the only one to oppose this view. His papers were, however, ignored. The only warning against accepting Gravitz's views too blindly, that I can find in the English language, is in a paper by Mr. Targett,[19] in 1896, in which he states that he has only found one such tumour in five years, of which he was convinced that it grew from a suprarenal rest. Quite recently Stœrck[17] has written an exhaustive paper, in which, after due consideration of the chemical and anatomical features of these tumours, he comes to the conclusion that they are formed not from suprarenal inclusions, but from the renal tubules themselves.

Before committing oneself one way or the other, it will be well to review the main anatomical and histological features of the hypernephromata.

They are nodular tumours which occupy, when small, the superficial cortical part of the kidney. They are more or less rounded encapsuled new-growths, consisting of lobules of a soft parenchyma separated by fibrous trabeculæ. Their most characteristic feature is their yellow colour, which is often rendered darker by hæmorrhage. They show a marked tendency to grow through the substance of the kidney into the pelvis, which they often break through, thus giving rise to profuse hæmaturia.

An hypernephroma may occupy either pole or the middle of the kidney. The remaining kidney substance is then pushed aside by it.

Metastases occur frequently by the blood-stream.

The smallest hypernephroma we have observed at post-mortems (1907—341) was an irregular encapsuled nodule, 1 by $\frac{1}{2}$ cm. in diameter, which lay in the most superficial part of the cortex, near the upper pole of the kidney, and projected considerably above its surface.

Microscopic examination reveals an appearance which, at first sight, strongly resembles the tissue of the suprarenal cortex. These are rounded solid acini of epithelial cells, whose protoplasm is extensively vacuolated, and often reduced to a ring around the cell and a few thin threads traversing its substance. These acini are separated from each other by thin-walled capillaries, whose spindle-shaped nuclei often form their only covering. The acini may grow so as to form large masses of cells which are closely packed together and contain no true central lumen, any existing cavitation being obviously due to central necrosis. In the larger acini giant cells are said to be of frequent occurrence. In our specimens, however, they were, on the whole, rare. The only case which showed them well was Mr. Golding–Bird's case, figured in the 59th volume of these Reports. These, then, are the characteristic microscopic features of these tumours; features that induced Gravitz, and most writers after him, to believe that they represent new growths arising in aberrant suprarenal tissue.

If, now, sections taken from many parts of as many of these tumours as possible be examined, remarkable appearances will often be encountered. The connective tissue often proliferates and occludes the capillaries, so that the acini over large areas are separated by definite and even stout connective tissue septa. The epithelium is by no means always vacuolated, but in many parts consists of large homogeneously staining cells, which bear not the faintest resemblance to the epithelium of the suprarenal. This feature is well illustrated in Mr. Golding–Bird's case just mentioned. Again, the smaller acini often consist of spaces lined by a layer of cubical or columnar cells whose free ends

project in a clubbed manner into the central-lumen. This lumen is not caused by the disappearance of central cells, and may even be occupied by a colloid material, identical in appearance and in staining reactions with the secretion so often found in the kidney tubules. I have observed this appearance in the centre of the large hypernephroma of the right kidney of a woman of forty, whose left organ contained the embryonic tumour already described. Here it could not possibly have been produced by the inclusion of renal tubules, since the tumour was totally encap-suled and showed no signs of malignant or even active growth. Not only do the acini often enclose a lumen, but the epithelium may grow into this lumen in the shape of papillæ, which often contain a delicate connective tissue core, surrounding a central capillary. When, as often is the case, the cells lining these papillæ are tall and columnar, the resemblance to an adenoma of the kidney is very striking.

The most complete case, however, was one of Dr. Hale White's, which has already been described and figured,* and which, therefore, need not be described at length here. A typical hypernephroma was removed by operation. A large local recurrence occurred, which presented a marked papillary structure, consisting of thin-walled blood-vessels surrounded by a small amount of connective tissue, and covered by many layers of columnar and cubical epithelium. The drawings of this case bring out the differences between the original tumour and the recurrence very plainly. Here there could not be the slightest doubt that the growth had originated in the kidney substance itself.

Not only do these hypernephromata show such appearances, but occasionally a tumour, which no one would call a hyper-nephroma, presents areas which closely resemble suprarenal tissue. Such an appearance has even been observed in the embryonic tumour of the left kidney of a woman of 40, which has been described above. It is possible that the tumour of the right kidney of this case may have been of a similar nature.

*Journal of Pathology and Bacteriology, 1909.

Such papillary appearances strongly suggest that the tumours in which they occur are formed from the kidney substance itself, and not from aberrant suprarenal tissue. The suprarenal is a solid body with no external secretion, whereas the kidney consists of a mass of tubules which are often, in pathological conditions, distended by retained secretion. The kidney frequently gives rise to adenomata, which show a marked papillary arrangement. Although I believe most of these papillæ to be false, yet true papillæ occur. As stated above, the epithelium of real adenomata is occasionally extensively vacuolated.

It would take too long to review Stœrck's researches on the nature of the substance occupying these vacuoles. He comes to the conclusion that in hypernephromata they are caused almost entirely by hydropic distension, since a very pale tumour of this nature may contain little or no fat.

Primary carcinomata of the suprarenal are rare. I have had the opportunity of examining but one case, which was a spheroidal-celled carcinoma, and in no way resembled a hypernephroma of the kidney.

On taking all these facts into consideration, it seems to me that many, at least, of the so-called "hypernephromata" of the kidney are really renal and not suprarenal tumours. Fascinating though the theory may be that in the kidney, where displaced suprarenal tissue is so common, this tissue gives rise frequently to tumour formation in the sense of Cohnheim's theory, yet it will be well for these tumours to be carefully examined and their varying microscopic appearance to be taken into account before we too blindly accept their origin from displaced suprarenal rests.

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19. **Targett, J. H.**—Trans. of the Pathological Society, 1896, xlvii., p. 122.

LIST

OF

GENTLEMEN EDUCATED AT GUY'S HOSPITAL

WHO HAVE PASSED THE

EXAMINATIONS OF THE SEVERAL UNIVERSITIES, COLLEGES,

&c., &c.,

IN THE YEAR 1908.

University of London.

Examination for the Degree of Doctor of Medicine

Branch I.—*Medicine.*
H. F. Vandermin (Qualified for Gold Medal).
Branch II.—*Pathology.*
R. W. Allen.

Branch IV.—*Midwifery and Diseases of Women.*

F. Alcock.	C. A. L. Meyer.
E. G. Goldie.	D. L. Morgan.

E. W. Strange.

Branch VI.—*Tropical Medicine.*
O. Marriott.

Examination for the Degree of Doctor of Science.

Physiology.
David Forsyth, M.D.

Examination for the M.B., B.S. Degrees.

May.
A. N. Leeming (Distinguished in Medicine).
Pass.

G. N. Bartlett.	O. Marriott.
E. L. Martyn Lobb.	H. Stott.

Supplementary Pass List.

Group I.—*Medicine, Pathology, and Forensic Medicine.*

W. Johnson.	W. P. Purdom.

Group II.—*Surgery, Midwifery, and Diseases of Women.*

T. Evans.	F. W. Hogarth.

October.

Obtained Honours.

(a, d, e) H. O. Brookhouse. | (a) H. I. Janmahomed.
   (Gold Medal). | (a) V. Townrow.

(a) *Distinguished in Medicine.*
(d) *Distinguished in Surgery.*
(e) *Distinguished in Midwifery and Diseases of Women.*

Pass.

C. A. Basker.	K. H. Hole.	D. Reynolds.
G. B. Harland.	W. Johnson.	H. A. Sanford.
H. J. Henderson.	H. B. Kent.	

Supplementary Pass List.

Group I.—*Medicine, Pathology, and Forensic Medicine.*

R. C. V. Edsall. | W. P. H. Munden.

Group II.—*Surgery, Midwifery, and Diseases of Women.*

Intermediate Examination in Medicine.

January.

G. B. Cockrem.	W. E. Fox.	R. Stout.
F. A. Dick.	T. Lewis Jones.	*G. Y. Thomson.
J. A. Edmund.	E. A. Penny.	C. Witts.

* *Distinguished in Pharmacology.*

July.

G. A. Blake.	C. D. Killpack.	*A. H. Todd.
F. Cook.	G. T. Mullally.	A. D. Vazquez.
A. H. Gool.	E. G. Schlesinger.	

* *Distinguished in Physiology.*

Preliminary Scientific Examination.

January.

Part I.—*Inorganic Chemistry, Experimental Physics, and Biology.*

H. Webb.

Inorganic Chemistry and Experimental Physics.

(b) R. Creasy. | W. Robinson.

Inorganic Chemistry and Biology.

(p) W. A. Young.

Inorganic Chemistry only.

(p,b) W. S. George.

Experimental Physics only.

(c) H. Mather.

Biology only.

(c,p) F. D. Annesley.

(b) *Has already passed in Biology.*
(c) *Has already passed in Organic Chemistry.*
(p) *Has already passed in Experimental Physics.*

University of Oxford.

Second M.B. Examination.

C. G. Douglas. | N. Flower. | D. B. Todd.

University of Cambridge.

Degree of Doctor of Medicine.

R. E. French.

Third Examination for the Medical and Surgical Degrees.

Part II.

H. Chapple. | L. T. Dean. | T. N. Wood.
A. H. Crook. | H. Lee. |

Part I.

H. L. Attwater. | K. T. Khong. | A. E. Rayner.
H. L. Duke. | W. Ledlie. | C. F. Searle.

Second Examination for the Medical and Surgical Degrees.

G. W. M. Andrew. | G. W. B. Garrett. | A. S. Seabrooke.
A. H. Birks. | R. Heaton. |

Tropical Medicine.

C. A. L. Meyer.

Sanitary Science.

Captain T. C. Lucas, R.A.M.C.
E. P. Minett.

University of Durham.

Final Examination for the Degrees of M.B. and B.S.

J. F. Young.

Third Examination for the Degrees of M.B. and B.S.

W. Reynolds.

Second Examination for the Degrees of M.B. and B.S.

E. W. Blake. | H. L. James. | G. E. W. Lacey.
                    H. F. Stephens

First Examination for the Degrees of M.B. and B.S.

Chemistry and Physics.

H. G. DODD.

Royal College of Physicians of London.

Elected to the Fellowship.
Theodore Fisher, M.D. Lond.

Examination for the Membership.
Hector C. Cameron, M.D. Camb. | R. A. Chisholm, M.B. Oxon.
C. E. Iredell, M.D. Lond.

Final Examination for the Licence.

January.
H. J. B. Cane	E. L. Martyn Lobb	H. Stott
A. F. W. Denning	C. H. Marshall	G. F. Syms
A. L. Foster	J. B. Martin	

April.
A. Davidson	A. V. Ledger	H. A. Sanford
A. W. Ewing	B. Muir	B. Wallis
F. J. Kolaporewala	C. E. Price	C. S. E. Wright

July.
H. O. Brookhouse	R. Franklin	H. I. Janmahomed
H. B. Carter	P. C. Higgins	W. Johnson
H. Chapple	F. W. Hogarth	H. B. Kent
L. T. Dean	K. H. Hole	V. Townrow
J. B. Dunning	C. C. Holman	

October.
F. R. L. Atkins	J. W. Grice	P. Seymour Price
M. E. Ball	H. C. Lucey	D. Reynolds
A. H. Crook	E. L. W. Mandel	L. L. C. Reynolds
S. J. Darke	M. K. Nelson	R. P. Roberts
M. R. Dobson	H. E. Perkins	A. H. V. St. John
F. Halcombe Fuller	W. G. Pinching	J. Walker
H. N. Greaves	C. M. Plumptre	C. A. Wood

Royal College of Surgeons of England.

Final Examination for the Fellowship.
R. Davies-Colley | B. Glendining
S. W. Daw | W. Welchman

Primary Examination for the Fellowship.
F. Cook | B. Glendining | G. Maxted

Final Examination for the Membership.

January,
H. J. B. Cane	E. L. Martyn Lobb	H. Stott
A. F. W. Denning	C. H. Marshall	G. F. Syms
A. L. Foster	J. B. Martin	

April.
A. Davidson	A. V. Ledger	H. A. Sanford
A. W. Ewing	B. Muir	B. Wallis
F. J. Kolaporewala	C. E. Price	C. S. E. Wright

July.

H. O. Brookhouse	R. Franklin	H. I. Janmahomed
H. B. Carter	P. C. Higgins	W. Johnson
H. Chapple	F. W. Hogarth	H. B. Kent
L. T. Dean	K. H. Hole	V. Townrow
J. B. Dunning	C. C. Holman	

October.

F. R. L. Atkins	J. W. Grice	P. Seymour Price
M. E. Ball	H. C. Lucey	D. Reynolds
A. H. Crook	E. L. W. Mandel	L. L. C. Reynolds
S. J. Darke	M. K. Nelson	R. P. Roberts
M. R. Dobson	H. E. Perkins	A. H. V. St. John
F. Holcombe Fuller	W. G. Pinching	J. Walker
H. N. Greaves	C. M. Plumptre	C. A. Wood

EXAMINATIONS FOR THE L.D.S. ENGLAND.

Final Examination.

May.

Parts I. and II.

P. S. Harrison	L. A. B. King	E. Smith
W. A. James	A. L. Saul	E. E. Solomon

Part I. only

S. Wilson Charles	L. B. Griffin	A. Samuel
P. C. Charlton	R. W. Morrell	H. G. Spain
A. Cohen	H. S. Pugh	W. E. A. Tibbalds

Part II. only.

*W. F. Boxall	*C. C. Jones	*W. S. Rutter
*S. W. Chetwood	*V. Masters	*H. P. Tait
*F. N. Doubleday	*W. Grant Oliver	*R. M. Wormald
*A. M. Henry	*J. R. Palmer	

November.

Parts I. and II.

H. V. Gibbons	W. A. Hodgson	D. B. Tasker
W. E. Guilding	W. S. Lacey	E. A. Tomes

Part I. only.

N. D. Clarke	D. Y. Hylton	A. MacDonald Watson
J. D. George	R. C. Morgan	

Part II. only.

*S. Wilson Charles	*F. O. Hume	*H. S. Pugh
*P. C. Charlton	*N. James	*W. E. A. Tibbalds
*L. B. Griffin	*R. W. Morrell	*W. F. Whiteley

* Denotes completion of **Examination.**

First Professional Examination.

May.

Mechanical Dentistry and Dental Metallurgy.

H. F. Barge	C. J. Henry	C. H. G. Penny
C. H. Barnett	S. W. Ingram	J. M. Pomeroy
C. H. Bradnam	H. L. Messenger	J. A. W. Stuart
C. F. Constant	W. C. Miller	W. E. Tanner
T. L. Fiddick	C. G. Morris	W. A. Thompson
F. L. Furse	H. S. Morris	H. Thornton
H. H. Glover	C. F. Moxley	N. S. Heegaard Warner

Mechanical Dentistry only.

G. V. Dymott	*F. H. Edey	R. Edgar

Dental Metallurgy only.

R. B. Campion	R. Curle	K. G. Hoby

November.

Mechanical Dentistry and Dental Metallurgy.

W. K. Fry	A. Stanley Morgan	R. W. Powell
F. S. Glover	P. H. Orton	G. B. Pritchard
L. P. Harris	F. W. Paul	C. F. L. Ruck
E. P. Hudson	G. E. H. H. Phillips	C. F. Snow
E. A. C. Knox-Davies	A. G. Poock	

Mechanical Dentistry only.

*R. B. Campion	A. E. F. Peaty	W. H. Wotton
H. Harrison	G. H. Rowley	E. O. Yeobury
*K. G. Hoby	A. E. V. Spill	

Dental Metallurgy only.

*G. V. Dymott	F. A. Jaques	G. E. Rowstron
*N. Edgar	A. P. L. Johnson	J. H. Wiles
J. E. R. Evans	C. A. Pollard	

Preliminary Science Examination.

January.

R. B. Adams	‡T. L. Fiddick	S. W. Ingram
	H. Thornton	

March and April.

R. G. Farrington	K. G. Hoby	P. H. Orton
†T. L. Fiddick	F. A. Jaques	R. W. Powell

July.

F. S. Glover	A. Stanley Morgan	D. Wain
H. Harrison	F. W. Paul	‡E. O. Yerbury

* Denotes completion of Examination.
† Chemistry only.   ‡ Physics only.

Society of Apothecaries. London.

R. B. Dawson	J. K. A. Helm	O. C. H. L. Moll
	E. H. Patterson	

Medical Department, Royal Navy.

A. T. Rivers.

Royal Army Medical Corps.

W. H. S. Burney	M. Leckie	S. McK. Saunders
A. L. Foster	D. Pottinger	

Indian Medical Service.

A. S. Khan | H. Stott

MEDALLISTS AND PRIZEMEN.

July, 1909.

Open Scholarships in Arts.

Arthur Joseph Eagleton Smith, Rugby School, £100.
Henry William Evans, Bedford Modern School, £50.

Open Scholarships in Science.

John Frederick Gwyther Richards, Victoria College, New Zealand, and
　　Preliminary Science Class, Guy's Hospital, £150.
William Leslie Webb, Preliminary Science Class, Guy's Hospital, £60.
George Sefton Miller, Preliminary Science Class, Guy's Hospital, Certificate.

Scholarship for University Students.

Nathan Mutch, B.A., Emmanuel College, Cambridge, £50.
Harold Wordsworth Barber, B.A., Clare College, Cambridge, Certificate.

Open Scholarships in Dental Mechanics.

October, 1908, William Hector Wotton, £20.
May, 1909, Guy William Enston Holloway, £20.

Junior Proficiency Prizes.

William Edward Tanner, £20.
William Stanley George, £15.

The Beaney Prize for Pathology (1908).

Edward Leslie Martyn Lobb, £34.

The Michael Harris Prize for Anatomy.

William Edward Tanner, £10.
William Stanley George, Certificate.

The Hilton Prize for Dissections (1908).

Geoffrey Marshall, £5.

The Wooldridge Memorial Prize for Physiology

William Stanley George, £10.
William Edward Tanner, Certificate.

Dental Prizes.

First Year's Students.

Edward Palmer Hudson, £10.

Wilfrid Stephen Ollis, } Equal Certificates.
William Hector Wotton, }

Practical Dentistry Prize.

Hubert Ernest Shepherd, £10.
Clement John Henry, Certificate.

Newland-Pedley Gold Medal for Practical Dentistry.

George Evan Henry Holt Phillips.
Hubert Ernest Shepherd, Certificate.

Golding-Bird Gold Medal and Scholarship in Bacteriology.

William Henry Catto, £20.
Habibmia Ismail Janmahomed, Certificate.

Treasurer's Gold Medal for Clinical Medicine.

Habibmia Ismail Janmahomed. ·

THE PHYSICAL SOCIETY.

Honorary President.—Sir Samuel Wilks, Bart., M.D., LL.D., F.R.S.

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Hon. Secretaries.—W. M. Mollison, M.C., C. H. Rippmann, M.A.

Session 1908–1909.—The Society's prize of £10 for the best essay read during the Session was awarded to Dr. E. P. Minett for his paper, " An Experimental Feeding Trial in Relation to Epidemic Enteritis."

The Treasurer's prize of £5 was gained by Mr. H. Stott, for his paper on " Present-day Treatment of Syphilis : its Special Value in Prophylaxis, and in the Prevention of Recurrence."

Mr. E. A. Penny received the prize of £5 for showing the best specimens of scientific interest during the Session.

CLINICAL APPOINTMENTS HELD DURING THE YEAR 1908.

HOUSE PHYSICIANS.

G. W. Goodhart	W. W. Cook	E. P. H. Joynt
C. B. Ticehurst	B. K. Nutman	C. H. Rippmann
B. H. Palmer	M. M. Earle	J. N. Watson
	H. J. Henderson	

HOUSE SURGEONS.

J. T. Smalley	H. A. Sanford	E. B. Hinde
R. R. Walker	J. S. Cooper	K. H. Digby
G. W. Dryland	N. Flower	G. F. Stebbing
	G. F. Syms	

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E. B. Hinde	W. W. Cook	H. J. Henderson
A. T. Densham	R. G. Chase	C. C. Holman
B. Wallis	A. W. Ewing	P. S. Price
M. E. Ball	H. E. Perkins	

OUT-PATIENTS' OFFICERS.

M. M. Earle	N. Flower	W. P. H. Munden
J. N. Watson	G. W. Dryland	E. B. Hinde
E. P. H. Joynt	B. H. Palmer	R. G. Chase
W. W. Cook	H. J. Henderson	G. F. Syms
H. A. Sanford	H. J. Carlyll	A. N. Leeming
E. L. M. Lobb	St. J. A. M. Tolhurst	

OBSTETRIC RESIDENTS.

H. F. Vaudermin	W. H. Trethowan	H. F. Joynt
J. F. Young	L. Croft	C. B. Ticehurst
K. H. Digby	A. S. M. Palmer	

CLINICAL ASSISTANTS.

C. A. Basker	H. B. Carlyll	J. W. Grice
H. Stott	P. S. Price	G. F. Syms
W. W. Cook	A. T. Densham	H. J. Henderson
E. P. H. Joynt	A. N. Leeming	B. H. Palmer
M. E. Ball	A. W. Ewing	W. L. M. Lobb
H. E. Perkins	H. A. Sanford	St. J. A. M. Tolhurst
L. T. Dean	W. Johnson	W. G. Pinching
C. M. Plumptre	V. Townrow	B. Wallis

CLINICAL ASSISTANTS IN THE MEDICAL WARDS.

H. I. Janmahomed	C. C. Holman	W. E. Wallis
W. Johnson	S. McK. Saunders	F. Morres
C. D. Roberts	S. H. Browning	H. Lee
F. J. Wheeler	M. M. Adams	T. F. Brown
H. Shahin	A. H. Crook	C. F. Searle

CLINICAL ASSISTANTS IN THE SURGICAL WARDS.

R. G. Oram	K. H. Hole	C. H. Mills
S. H. Browning	L. T. Baker	E. P. H. Hughes

CLINICAL ASSISTANTS IN MEDICAL OUT-PATIENTS.

D. Reynolds	E. R. Stone	E. A. Collins
D. Allan	H. Shahin	S. H. Browning
P. V. G. Pedrick		

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J. L. Johnston	H. Steinbach	C. H. Crump
H. F. Percival	A. L. Fitzmaurice	A. E. Rayner
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A. A. Greenwood	J. L. Atkinson	G. F. Haycraft
J. R. Perdrau	M. M. Adams	V. T. P. Webster
H. L. Attwater	H. L. Duke	R. C. H. Francis
W. E. Williams	F. D. Saner	W. S. Kidd
A. H. G. Burton	F. C. Endean	H. Steinbach
J. L. Johnston	A. L. Fitzmaurice	H. Platts
C. C. Tudge	W. H. Catto	G. H. Peall
W. Ledlie	D. A. Mitchell	E. L. Elliott
W. L. Hibbert	R. P. Ballard	C. Weller
N. L. Reader	W. H. Watson	F. Killard-Leavey
M. A. E. Duvivier	C. Witts	F. S. D. Berry
	D. A. Mitchell	

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H. B. Carter
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F. R. L. Atkins
L. T. Dean
E. L. M. Lobb
W. E. Wallis
J. Walker
A. E. Lees
K. H. Hole
A. C. Schulenberg
A. D. Williams

C. A. Wood
W. Johnson
R. B. Dawson
R. P. M. Roberts
H. E. H. Mitchell
T. F. Brown
E. R. Stone
H. W. Heasman
H. R. Bastard
C. M. Plumptre

F. J. Wheeler
F. J. Kolaporewala
M. E. Ball
P. Kolaporewala
H. I. Janmahomed
D. C. Druitt
M. A. Rahman
T. Evans
R. A. Rankine
H. L. Duke

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E. L. J. Lobb
E. R. Stone
S. K. Poole
F. J. Wheeler
S. J. Darke

W. Johnson
H. E. Perkins
H. C. Lucey
H. R. Mullins
J. Walker
H. Shahin
H. O. Brookhouse
R. A. Rankine

M. A. Rahman
H. I. Janmahomed
H. B. Carter
L. L. C. Reynolds
L. W. Evans
L. Mandel
A. H. Crook
C. A. Wood

MEDICAL WARD CLERKS.

W. S. Kidd
W. E. Williams
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H. G. Rice
F. D. Saner
D. C. Lloyd
J. G. Saner
A. C. Schulenberg
C. H. Crump
H. Steinbach
R. P. Ballard
A. Neville Cox
G. H. Hunt
E. L. Elliott
W. G. Tucker
J. Pryce Davies
T. T. O'Callaghan
F. A. Dick
C. E. Reckitt
T. Lewis Jones
W. E. Fox
R. Montgomery
A. D. Vazquez
A. L. Gardiner
E. Biliing
A. S. Roe

H. Platts
D. A. Mitchell
F. C. Endean
C. C. Tudge
W. Ledlie
H. W. Doll
J. W. Williams
W. T. Chaning-Pearce
W. H. Watson
A. L. Fitzmaurice
A. H. G. Burton
M. A. E. Duvivier
H. Gardiner
J. H. Owen
H. R. Greaves
C. Witts
G. B. Cockrem
M. M. Munden
G. Dunderdale
M. C. Thavara
J. A. Edmonds
W. E. Levinson
H. F. Renton
P. E. H. Patey
R. Stout
G. C. Lowe
B. J. Verver

W. L. Hibbert
C. Weller
F. S. Adams
T. J. Killard-Leavey
H. L. Attwater
H. Gardiner
T. D. Stout
K. T. Khong
N. A. D. Sharp
J. L. Johnston
R. C. H. Francis
F. S. D. Berry
W. Reynolds
N. L. H. Reader
P. C. Field
B. McDermott
W. H. T. Jones
E. A. Penny
G. Maxted
G. Y. Thomson
A. L. Saul
H. F. Stephens
G. E. W. Lacey
H. G. Blackman
E. P. Poulton

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J. Pryce Davies
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G. V. Thomson
R. Montgomery
T. T. O'Callaghan
W. H. T. Jones
T. D. Stout
J. G. Saner
K. T. Khong
H. W. Doll
E. P. Poulton
B. T. Verver
G. C. Lowe
A. H. Todd
C. D. Killpack
G. L. Preston
H. W. Barber
A. C. Jepson
J. M. Jarvie
L. C. Irvine
T. S. Sharpley

G. B. Cookrem
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A. D. Vazquez
H. F. Renton
C. E. Reckitt
G. E. W. Lacey
F. S. Adams
J. W. Williams
G. Dunderdale
R. Stout
R. Heaton
H. G. Blackman
W. P. Vicary
G. A. Blake
M. C. Wall
F. B. Bull
A. M. Bodkin
H. V. Leigh
H. D. Depree
N. Mutch
C. M. Ryley

T. Lewis Jones
M. M. Munden
J. A. Edmond
E. A. Penny
W. E. Levinson
H. F. Stephens
H. G. Rice
W. T. Chaning Pearce
D. C. Lloyd
A. S. Roe
E. Billing
A. L. Gardner
G. T. Mullally
L. C. W. Cane
H. H. Davis
H. L. James
J. H. Campain
B. Blackwood
A. H. Gool
J. A. Delmege
G. R. Hind

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W. G. Tucker
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C. Witts
H. L. Attwater
H. Platts
W. S. Kidd
W. H. Catto
F. S. Adams
K. T. Khong
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G. B. Cockrem
G. Maxted
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W. Ledlie
H. W. Doll
W. E. Williams
H. Gardner
T. D. M. Stout
E. A. Penny
R. Montgomery
T. Lewis Jones
W. H. Talfourd Jones
J. Pryce Davies
C. E. Reckitt

M. M. Munden
P. E. Patey
C. McDermott
R. P. Ballard
W. Reynolds
F. C. Endean
D. A. Mitchell
W. E. Williams
C. C. Tudge
C. Weller
W. T. Chaning Pearce
A. Neville Cox
H. G. Rice
H. F. Stephens
G. E. W. Lacey
H. F. Renton
W. E. Levinson
G. Dunderdale
M. C. Thavara

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M. M. Adams

H. Daw
W. H. Talfourd Jones
G. Marshall

F. G. Lloyd
A. L. Saul

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F. W. Hogarth	F. J. Wheeler	H. I. Janmahomed
H. R. Kent	A. H. Crook	H. C. Lucey
C. M. Plumptre	A. E. Lees	T. F. Brown
L. Bromley	C. C. Holman	R. A. Rankine

CLERKS IN THE SKIN DEPARTMENT.

G. H. Peall	R. C. H. Francis	D. Isaacs
	E. L. Elliott	

AURAL SURGEONS' DRESSERS

S. J. Darke	V. P. Hutchinson	D. Allan
C. H. Marshall	F. J. Cutler	M. A. Rahman
L. W. Evans	M. M. Adams	H. V. St. John
H. R. Mullins	R. A. Rankine	

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M. Cowasjee	J. L. Johnston	W. L. Hibbert
A. H. G. Burton	J. Walker	C. C. Holman
A. A. Greenwood	V. Townrow	A. D. Williams
J. Atkinson	G. F. Haycraft	J. R. Perdrau
R. M. Barron	R. A. Rankine	H. B. Kent
H. I. Janmahomed	T. Evans	A. E. Lees
H. Lee	L. Mandel	D. Allan
S. J. Darke	A. Cheesman	A. R. Khalakdina
C. G. Sprague	S. S. Brooke	G. H. Hunt
M. M. Adams	W. E. Wallis	A. C. Schulenberg
W. G. Tucker	S. H. Browning	A. E. Rayner
C. H. Crump	H. F. Percival	L. Bromley
F. Kahlenberg	P. C. Field	H. L. Duke
W. H. Catto	E. P. Poulton	V. T. P. Webster
W. Ledlie	J. H. Owen	T. F. Brown
	T. Stansfield	

OBSTETRIC DRESSERS.

H. Chapple	H. W. Heasman	R. P. M. Roberts
H. C. Lucey	S. J. Darke	T. F. Brown
H. O. Brookhouse	A. F. W. Denning	K. H. Hole
F. C. V. Thompson	F. W. Hogarth	H. B. Carlyll
R. A. Rankine	F. J. Wheeler	H. A. Sanford
C. M. Plumptre	H. B. Kent	V. Townrow
D. Reynolds	L. T. Dean	H. L. Duke
A. H. Crook	H. R. Bastard	J. R. Perdrau
C. A. Wood	C. F. Searle	T. Killard-Leavey
A. C. Schulenberg	T. Stansfield	W. H. Watson
C. E. Holman	J. L. Atkinson	A. L. Fitzmaurice
G. F. Haycraft	A. A. Greenwood	N. A. D. Sharp
A. H. G. Burton	W. S. Kidd	

CLERKS TO ANÆSTHETISTS.

C. A. Wood	J. Walker	J. L. Atkinson
H. I. Janmahomed	E. A. Collins	H. B. Kent
G. F. Haycraft	J. K. Helm	S. J. Darke
C. O. Holman	H. Chapple	L. T. Dean
W. Johnson	A. H. Crook	D. Allan
K. H. Hole	M. Cowasjee	S. H. Browning
T. Stansfield	A. Cheesman	V. Townrow
L. Mandel	R. C. F. Francis	D. C. Roberts
R. A. Rankine	A. H. G. Burton	L. W. Evans
C. G. Sprague	C. M. Plumptre	T. N. Wood
R. G. Oram	S. S. Brook	L. K. Edmeades
F. H. Edey	A. R. Khalakdina	M. M. Adams
J. R. Perdrau	V. P. Hutchinson	D. C. Druitt
F. R. L. Atkins	H. L. Duke	M. A. E. Duvivier
A. E. Lees	S. H. Browning	T. F. Brown
A. L. George	W. H. Catto	W. T. Clark
W. H. Watson	C. M. Plumptre	F. J. Killard-Leavey
F. Kahlenberg	A. E. Rayner	H. F. Percival
C. H. Mills	C. F. Searle	C. H. Crump
T. Evans	F. J. Cutler	P. C. Field
L. L. C. Reynolds	J. H. Owen	R. P. M. Roberts
H. Shahin	C. Weller	W. E. Wallis
H. R. Bastard	L. Bromley	W. Ledlie
J. L. Johnston	N. A. D. Sharp	V. T. P. Webster
A. D. Williams	E. L. Elliott	G. H. Hunt
Q. Richardson	G. Y. Thomson	
F. C. Endean	A. A. Greenwood	

DENTAL SCHOOL

CLINICAL APPOINTMENTS HELD DURING THE YEAR 1908.

HOUSE SURGEONS.

R. J. Gibbings	G. Hunt	I. S. Spain
F. N. Doubleday	W. Grant Oliver	E. E. Solomon

ASSISTANT HOUSE SURGEONS.

E. E. Solomon	C. C. Jones	H. V. Gibbons
A. L. Saul	E. A. Tomes	J. R. Palmer
W. S. Lacey	J. Roberts	W. E. A. Tibbalds
S. W. Charles	L. B. Griffin	W. A. Hodgson

ASSISTANT DEMONSTRATORS IN DENTAL MECHANICS.

S. W. Charles	W. S. Lacey	A. J. Reynolds
	E. A. Tomes	

ASSISTANT DEMONSTRATORS IN DENTAL METALLURGY.

J. Roberts	L. B. Griffin	G. H. Hickman
	N. D. Clarke	

ASSISTANT DEMONSTRATORS IN DENTAL MICROSCOPY.

W. E. A. Tibbalds	W. A. Hodgson	F. B. Bull

DRESSERS IN THE GAS ROOM.

A. J. Schaefer	R. W. Powell	C. F. L. Ruck
H. H. Glover	A. P. L. Johnson	C. H. Bradnam
P. S. Humm	N. Edgar	C. H. Brangwin
W. H. Edmonds	S. W. Charles	A. Samuel
E. A. Tomes	A. Mc. D. Watson	W. A. Hodgson
A. P. Marsh	P. S. Harrison	W. A. James
A. Cohen	A. L. Saul	A. M. Henry
G. H. Hickman	H. G. Spain	E. J. Archer
P. R. Helyar	J. Roberts	S. W. Chetwood
N. D. Clarke	W. S. Lacey	F. H. Edey
J. A. W. Stuart	H. S. Morris	G. V. Dymott
H. S. Pugh	F. A. Lowe	G. H. Rowley
A. J. Reynolds	W. E. A. Tibbalds	W. E. Watson
L. J. Kemp	H. E. Shepherd	H. Daw
J. M. Pomeroy	K. G. Hoby	H. Thornton
T. L. Fiddick	H. T. Peplow	A. E. F. Peaty
	F. L. Furse	

DRESSERS IN THE EXTRACTION ROOM.

C. H. Barnett	J. R. Pomeroy	K. G. Hoby
S. W. Ingram	H. T. Peplow	C. H. G. Penny
C. J. Henry	C. F. Moxley	G. H. Rowley
F. A. Lowe	H. F. Barge	A. J. Schaefer
J. A. W. Stuart	R. Curle	W. C. Miller
A. E. V. Spill	R. W. Powell	A. E. F. Peaty
N. Edgar	C. H. Brangwin	C. G. Morris
J. M. Pomeroy	C. F. L. Ruck	W. E. Tanner
C. H. Bradnam	F. A. Jaques	C. F. Constant
J. G. Richards	H. Daw	P. H. Orton
F. L. Fiddick	A. Samuel	H. Thornton
J. E. R. Evans	H. L. Messenger	C. A. Bollard
W. K. Fry	R. B. Campion	D. W. Wiseman
A. G. Poock	J. H. Wiles	A. E. C. Knox Davies
W. C. Miller	H. Harrison	A. W. Harris
J. H. Clapperton	S. W. Ingram	A. S. Morgan
F. W. Paul	C. F. Snow	E. O. Yerbury
E. P. Hudson	L. H. Pellow	L. P. Harris
G. B. Pritchard	C. E. Rice	H. C. Corke

CASUALTY DRESSERS.

W. H. Edmonds	S. W. Ingram	J. A. W. Stuart
P. S. Humm	A. P. L. Johnson	N. Edgar
A. McD. Watson	G. V. Dymott	H. S. Morris
C. H. Bradnam	H. H. Glover	C. G. Morris
C. F. L. Ruck	C. H. Brangwin	W. C. Miller
H. Thornton	F. L. Fiddick	C. F. Moxley
F. L. Furse	H. Daw	C. H. Barnett
A. E. F. Peaty	K. G. Hoby	G. E. H. Philips
H. T. Peplow	J. M. Pomeroy	R. W. Powell
C. J. Henry	N. S. H. Warner	A. E. V. Spill
J. G. Richards	F. A. Jaques	P. H. Orton

DRESSERS IN THE CONSERVATION ROOM.

F. N. Doubleday	A. E. V. Spill	H. T. Peplow
A. L. Saul	R. M. King	J. Roberts
D. B. Tasker	E. Smith	E. W. Sumpter
R. M. Wormald	E. A. Tomes	W. F. Boxall
L. J. Kemp	H. G. Spain	W. F. Whiteley
W. A. Hodgson	P. R. Helyar	W. H. Edmonds
W. S. Lacey	A. J. Reynolds	A. J. Schaefer
A. M. Henry	F. B. Bull	J. D. George
F. A. Lowe	G. H. Hickman	W. A. James
A. Samuel	R. C. Morgan	G. H. Rowley
S. W. Charles	W. E. Watson	W. J. Kennealey
H. S. Pugh	A. P. Marsh	R. W. Morrell
H. P. Tait	W. E. Tibbalds	F. H. Edey
S. W. Chetwood	F. O. Hume	N. D. Clarke
W. E. Guilding	A. Cohen	L. B. Griffin
L. A. B. King	P. Harrison	P. S. Humm
A. P. L. Johnson	D. Y. Hylton	M. J. Marks
H. S. Morris	J. A. W. Stuart	C. H. Bradnam
H. Daw	H. Thornton	W. A. Thompson
F. L. Furse	N. Edgar	G. V. Dymott
W. E. Watson	G. E. H. Phillips	H. E. Shepherd
W. E. Guilding	R. Curle	N. James
N. S. H. Warner	A. W. Harris	C. F. Moxley
P. H. Orton	W. H. Wiseman	C. H. Barnett
S. W. Ingram	N. Pomeroy	R. W. Powell
W. C. Miller	C. H. G. Penny	F. A. Jaques
	J. G. Richards	

GUY'S HOSPITAL.

MEDICAL AND SURGICAL STAFF.

1909.

Consulting Physicians.—SIR SAMUEL WILKS, BART., M.D., LL.D., F.R.S.; F. W. PAVY, M.D., LL.D., F.R.S.; P. H. PYE-SMITH, M.D., F.R.S.; J. F. GOODHART, M.D., LL.D.; F. TAYLOR, M.D.

Consulting Surgeons.—THOMAS BRYANT, M.Ch.; Sir H. G. HOWSE, M.S.; W. H. A. JACOBSON, M.Ch.; R. CLEMENT LUCAS, B.S.; C. H. GOLDING-BIRD, M.B.

Consulting Obstetric Physician.—A. L. GALABIN, M.D.

Consulting Physician for Mental Diseases.—G. H. SAVAGE, M.D.

Consulting Ophthalmic Surgeons.—C.HIGGENS,ESQ.; W.A.BRAILEY,M.D.

Consulting Aural Surgeon.—W. LAIDLAW PURVES, M.D.

Consulting Dental Surgeon.—F. NEWLAND-PEDLEY, ESQ.

Consulting Anæsthetist.—TOM BIRD, ESQ.

Physicians & Assistant Physicians.
W. HALE WHITE, M.D.
G. NEWTON PITT, M.D.
SIR E. COOPER PERRY, M.D.
L. E. SHAW, M.D.
J. FAWCETT, M.D.
A. P. BEDDARD, M.D.
H. S. FRENCH, M.D.
A. F. HERTZ, M.D.

Obstetric Physicians.
J. H. TARGETT, M.S.
G.BELLINGHAM SMITH,M.B.,B.S.

Physician for Mental Diseases.
MAURICE CRAIG, M.D.

Physician in Charge of Skin Department.
SIR E. COOPER PERRY, M.D.

Anæsthetists.
G. ROWELL, ESQ.
H. F. LANCASTER, M.D.
C. J. OGLE, ESQ.
H. M. PAGE, ESQ.
F. E. SHIPWAY, M.D.
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A. R. THOMPSON, M.B., Ch.M.
R. DAVIES-COLLEY, M.C.
H. C. CAMERON, M.B., B.C.
T. B. LAYTON, M.S.

Bacteriologist.
J. W. H. EYRE, M.D.

Medical Registrars and Tutors.
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C. H. RIPPMANN, M.B., B.C.

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L. A. DUNN, M.S.
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P. TURNER, M.S.

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A. W. ORMOND, ESQ.

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Surgeon in Charge of Aural Department.
P. TURNER, M.S.

Surgeon in Charge of Actino-Therapeutic Department.
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H. L. PILLIN, ESQ.
M. F. HOPSON, ESQ.

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J. L. PAYNE, ESQ.

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Warden of the College.
W. M. MOLLISON, M.C.

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Dean of the Medical School.
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1909.

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Surgery.

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Practical Surgery	T. B. LAYTON, M.S., AND K. H. DIGBY, M.B., B.S.
Surgical Revision Classes	P. TURNER, M.S.

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Practical Obstetrics	R. DAVIES-COLLEY, M.C.
Obstetric Revision Classes	G. BELLINGHAM SMITH, M.B., B.S.

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Morbid Anatomy (Demonstrations) in Post-mortem Room	J. FAWCETT, M.D., H. S. FRENCH, M.D. AND A. F. HERTZ, M.D.
Surgical Pathology (Demonstrations)	R. P. ROWLANDS, M.S.
Medical Pathology (Demonstrations)	J. FAWCETT, M.D.
General Pathology (Demonstrations)	A. E. BOYCOTT, M.D.

Ophthalmology.

Clinical Ophthalmology	THE OPHTHALMIC SURGEONS.
Ophthalmology (Lectures)	H. L. EASON, M.S., M.D.

Diseases of the Throat and Nose.

F. J. STEWARD, M.S.

Diseases of the Ear.

P. TURNER, M.S.

Diseases of the Skin.

SIR E. COOPER PERRY, M.D.

Dental Surgery.
W. WYNNE ROUW, ESQ.

Mental Diseases.
MAURICE CRAIG, M.D.

Materia Medica and Pharmacology.
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Pharmacology (Demonstration
                 Classes) J. H. RYFFEL, B.C.
Practical Pharmacy ...   .   THE HOSPITAL PHARMACIST.

Forensic Medicine.
H. S. FRENCH, M.D.
J. H. RYFFEL, B.C.
(Temporary Joint Lecturers.)

Hygiene and Public Health.
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Anaesthetics.
G. ROWELL, ESQ.

Bacteriology.
J. W. H. EYRE, M.D.

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                               FAGGE, M.S.
Practical Anatomy   ...   .   A. R. THOMPSON, M.B., Ch.M.,
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                            E. C. HUGHES, M.C.

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Practical Physiology ...   .   M. S. PEMBREY, M.D., J. H. RYFFEL,
                            M.A., B.C., AND E. L. KENNAWAY,
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                            B.Sc.

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Practical Physics   ...   .   R. W. MERRIMAN, B.A., B.Sc.

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Practical Biology   ...   .   W. YOUNGMAN, B.Sc., AND E. C. HUGHES,
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                            M. S. PEMBREY, M.D. (OXON.).
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The Hospital contains accommodation for 608 Patients, an additional 50 Beds having been opened on the Medical side of the Hospital.

Special Classes are held for Students preparing for the University and other Higher Examinations.

APPOINTMENTS.

All Hospital Appointments are made strictly in accordance with the merits of the Candidates, and without extra payment. There are 24 Resident Appointments open to Students of the Hospital annually without payment of additional fees, and numerous Non-resident Appointments in the general and special departments. The Queen Victoria Ward provides accommodation for gynæcological and maternity cases.

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Two Open Scholarships in Arts, one of the value of £100 open to Candidates under 20 years of age, and one of £50 open to Candidates under 25 years of age. Two Open Scholarships in Science, one of the value of £150, and another of £60, open to Candidates under 25 years of age. One Open Scholarship for University Students who have completed their study of Anatomy and Physiology, of the value of £50.

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The Residential College accommodates about 50 Students in addition to the Resident Staff of the Hospital. It contains a large Dining Hall, Reading Room, Library, and Gymnasium for the use of the Students' Club.

For Prospectus and further information, apply to the Dean, Dr. EASON, Guy's Hospital, London Bridge, S.E.

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1909.

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Dental Surgeons.
W. A. Maggs, L.R.C.P., M.R.C.S., L.D.S.E.
R. Wynne Rouw, L.R.C.P., M.R.C.S., L.D.S.E.
H. L. Pillin, L.D.S.E.
M. F. Hopson, L.D.S.E.

Assistant Dental Surgeons.
J. B. Parfitt, L.R.C.P., M.R.C.S. L.D.S.E.
J. L. Payne, L.R.C.P., M.R.C.S., L.D.S.E.

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F. J. Pearce, L.D.S.E.

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H. P. Aubrey, L.R.C.P., M.R.C.S., L.D.S.E.

Demonstrators of Prosthetic Dentistry.
S. W. Charles, L.D.S.E.

E. A. Tomes, L.D.S.E.

Anæsthetists.
H. F. Lancaster, M D.

A. R. Thompson, Ch.M., F.R.C.S.

C. J. Ogle, M.R.C.S.

R. Davies-Colley, M.B., M.C.

W. M. Mollison, M.C., F.R.C.S.

F. E. Shipway, M.D.

Lecturers.
Dental Anatomy and Physiology.—Mr. Maggs.
Dental Surgery and Pathology.—Mr. Wynne Rouw.
Practical Dental Mechanics.—Mr. Pillin.
Operative Dental Surgery.—Mr. Parfitt.
Dental Mechanics.—Mr. Payne.
Dental Materia Medica.—A. P. Beddard, M.D.
Dental Bacteriology.—J. W. H. Eyre, M.D.
Dental Microscopy.—Mr. E. B. Dowsett and Mr. E. L. Kennaway.
Dental Metallurgy.—J. Wade, D.Sc.
Practical Dental Metallurgy.—Mr. Hopson.
Curator of Dental Museum.—Mr. Dowsett.
Dean.—H. L. Eason, M.D., M.S.

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